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August 23, 2006

By Hand Delivery

Mary B. Graham, Esquire
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Re: Bavarian Nordic A/S v. Acambis Inc., C.A. No. 05-614-SLR

Dear Mary:

Enclosed herewith is your service copy of the First Amended Complaint of plaintiffs, Bavarian Nordic A/S and Anton Mayr, which we have filed pursuant to the August 21, 2006 Memorandum Order (see D.I. 83 at p.3, n.1).

We recognize that the August 21 Order also granted defendants' motion to dismiss the misappropriation of trade secrets claim (Count II). Please note that the allegations of Count II are included in the First Amended Complaint purely to forestall any argument that plaintiffs have voluntarily dropped that claim, and not to derogate the effect of the August 21 Order.

Sincerely,

Karen L. Pascale

Enclosure

cc: William D. Coston, Esquire (by e-mail and FedEx) (with enclosure)
Martin L. Saad, Esquire (by e-mail and FedEx) (with enclosure)
Edward A. Pennington, Esquire (by e-mail) (with enclosure)
Robert C. Bertin, Esquire (by e-mail) (with enclosure)
John W. Shaw, Esquire (with enclosure)

EXHIBIT 2

CONFIDENTIAL EXHIBIT

EXHIBIT 3

CONFIDENTIAL EXHIBIT

EXHIBIT 4

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EXHIBIT 5

CONFIDENTIAL EXHIBIT

EXHIBIT 6

Dtsch. med. Wschr. **99** (1974), 2386–2392

MVA Vaccination Against Smallpox

Clinical Tests with an Attenuated Live Vaccinia Virus Strain (MVA)

H. Stickl, V. Hochstein-Mintzel, A. Mayr, H. Ch. Huber, H. Schäfer and A. Holzner

Bavarian State Vaccination Institute and Institute for Microbiology and Infectious Diseases of Animals of the University of Munich

[see source for bilingual English summary]

Even today, a smallpox vaccination is still associated with a high risk. Post-vaccination complications, especially after an initial vaccination, are more common than with all other vaccinations apart from rabies vaccination.

For many years, various methods of reducing the complication rate with smallpox vaccinations have been proposed throughout the world. These include mainly simultaneous administration of γ-globulin or specific anti-vaccinia serum and so-called prevaccination using an inactive vaccine, mainly the vaccine antigen. The efficacy of these methods is disputed in the meantime with regard to adequate immune stimulus and from the standpoint of preventing complications.

For many years, an attenuated vaccinia virus has been under testing in animal experiments at the Bavarian State Vaccination Institute. This virus, which has been referred to in the course of these experiments as the “MVA” strain (modified vaccinia virus Ankara strain) has proven to be aviral in animal experiments. On the basis of findings on primates, it has been used to produce vaccine and has ultimately been used clinically on patients. The findings obtained in this regard are the subject matter of the present article.

Material and Methods

Vaccine

Virus strain. Vaccinia virus Ankara strain was attenuated by Mayr in continuous passages on cell cultures of embryonal chick fibroblasts. The attenuated virus was assigned the identification CVA-HFE. Its properties were characterized for the first time by Mayr and Munz [14] in the 371st passage. According to the results of experiments, the cultured virus differed significantly from the starting virus. The essential feature of the cultured virus was the great reduction in virulence in the animal experiment. Vaccinia virus strain CVA-FHE was taken over in the 516th passage by the Bavarian State Vaccination Institute and was continued on cell cultures of embryonal chick fibroblasts. The eggs used in these experiments came from the company TAD in Cuxhaven. According to certification of the supplier company, the chicken population is free of avian leukosis and other pathogenic microorganisms.

With regard to its use as a vaccine, vaccinia virus strain CVA-FHE has been subjective to comparative testing with vaccinia Elstree strain for virulence and immunogenicity [12, 15]. In these experiments, the low virulence of the CHA-HFE strain was confirmed, in particular its low neurovirulence. The immunogenicity of the CVA-HFE strain was weaker than that of the Elstree strain. At a suitable dose and with a suitable form of administration, however, formation of hemagglutination inhibiting and virus neutralizing antibodies could also be induced with the CVA-HFE strain. Monkeys of the *Macaca irus* and *Macaca mulatta* species were protected from the disease by immunization with the CVA-HFE strain after a test infection with *Variola vera*. In two preliminary studies, the effect of CVA-HFE strain on humans was tested [20, 23]. Intracutaneous injection of 0.1 mL virus suspension containing 2×10^5 infectious particles caused redness measuring approximately .2 × 2 cm and lasting for several days. There was no fever or any disturbance in general well-being. The conventional smallpox vaccination with Elstree strain Vaccinia virus, which was performed after 7 days, proceeded with the typical picture of a repeat vaccination.

Preparation of vaccine. Vaccine produced from the CVA-HFE strain was identified as MVA vaccine so the strain was renamed MVA strain Vaccinia virus. MVA stands for "modified Vaccinia virus Ankara strain." Material obtained from cell cultures was additionally identified as HFE, material from the chorioallantoic membrane received the additional CAM designation.

a) Production of the vaccine of the chorioallantoic membrane (MVA-CAM): The depressed chorioallantoic membrane of leukosis-free chick eggs incubated for 10 days was inoculated with 1000 infectious virus unit in a volume of 0.1 mL. After incubating the eggs for 48 hours at 37°C, the membranes were harvested, washed again in phosphate buffer NaCl solution and deep frozen. After thawing, the membranes were placed in a 10-fold amount (rate/volume) of McIlvaine buffer and homogenized with 10% Freon®. After centrifugation for 10 minutes at 800 g, the supernatant was sedimented in 1 hour at 10,000 g, the sedimented was suspended in the starting amount with McIlvaine buffer and centrifuged a second time at a high speed. The second sediment was the starting material for preparation of the vaccine. After suspension in McIlvaine buffer, the virus content was ascertained and adjusted to 4×10^6 infectious units per milliliter for appropriate dilution. The virus suspension was stabilized by adding 1% human serum albumin and freeze-dried in 0.5 mL portions.

b) Production of the vaccine from the cell culture: The cell cultures for replication of the virus were prepared from 12-day old chick embryos of leukosis-free eggs according to the standard technique. The growth medium contained yeast extract, lactalbumin and 10% calf serum. After 48 hours, the cell growth was complete and was washed with phosphate buffered saline solution and then inoculated. The virus concentration in the inoculation medium was 10^6 infectious units per milliliter. After incubating for 72 hours at 37°C, the medium was poured off, the cell growth was washed again and extracted with 20.0 mL McIlvaine buffer and then frozen. After thawing the dishes, further processing of the vaccine was performed as in the production of the virus from infected chorioallantoic membrane.

Shipping the vaccine. The vaccine was shipped at no cost on written request to clinics and to private doctors' practices. An original package contained 0.5 mL freeze-dried vaccine, enough for two vaccinations.

So far approximately 12,500 vials of MVA vaccine have been shipped. This corresponds to approximately 25,000 vaccine doses.

Use of the vaccine

According to experience in the pilot studies, the vaccine should be injected intracutaneously in a dose of 0.2 mL on the side surface of the forearm. Phosphate-buffered saline solution is used as the solvent for the dry vaccine solids. The MVA vaccination is performed as a "step vaccination," i.e., the vaccination with MVA vaccine is to be followed by a conventional smallpox vaccination in any case. The success of the conventional vaccination must be checked as usual by re-testing 8 days after the vaccination based on the traditional evaluation criteria: this was done because the requirements of the valid statutory vaccination law are not met by vaccination exclusively with the MVA strain.

Analysis of the vaccination results

Reporting forms. Each physician received a reporting form together with the vaccine with instructions to use the reporting form to record all observations that might be important for an evaluation of the safety and efficacy of this vaccine.

The reporting forms are divided into three sections. The first section contains information about the patient receiving the vaccination, the most important of which is the age at vaccination, divided (according to the conventional limit for being "above age" for smallpox vaccination) into a group with an age of more than three years and a group with an average of less than three years. The vaccination status was either initial vaccination or repeat vaccination. The question of a vaccination interval was not addressed because in this study value was placed mainly on the observation of initial vaccinations anyway. The vaccination indications were summarized according to their empirical frequency and also according to relevance for the evaluation of the safety of the method tested.

The second section of the reporting form contains questions about the observations after MVA vaccination. The local reaction should be described immediately after the injection and then 2 and 7 days after the injection.

The questions about possible disturbances in general well-being are deliberately formulated in an undifferentiated manner because our experience indicates that these questions are answered primarily by the layman.

The third section of the reporting form contains questions about the observations of the main cutaneous vaccination, differentiated essentially according to the local vaccination reaction and the systemic vaccination reaction. The questions about the local vaccination reaction differ from our usual classification according to "vesicular reaction," "pustular reaction," "nodular reaction," i.e., a, b and c reactions, because this classification is neither logical nor does it allow differentiation without any doubt among the various types of reactions. However, the reaction types proposed on the questionnaire:

Vesicles or pustules	without scab
Vesicles or pustules	with scab
Nodules (or infiltrate)	without scab
Nodules (or infiltrate)	with scab

should allow a satisfactory classification. In addition, this should largely objectify the difficult decision between initial vaccination and repeat vaccination. Only pustules without a scab or vesicles without a scab should be considered typical initial vaccination reactions in the analysis. In addition, the reaction types selected allow a classification into the reaction types proposed by the World Health Organization, i.e., "positive" ("major reaction"), "questionable" ("equivocal reaction") and negative.

The questions about concomitant symptoms of the vaccination are also very general in this section to facilitate the decision on the part of the evaluating physician as much as possible and thereby arrive at a clear conclusion.

Analysis[1]. Instead of the individual reporting forms, in many case a lump sum report of the vaccination results was given. Many of these reports contained only reports about the vaccination being fever-free and without complications. There was no analysis of these lump sum empirical reports. Nor were the individual questionnaires analyzed if they were not filled out adequately.

Seven thousand ninety-eight forms were available for statistical analysis. Any inadequate or unclear information was not evaluated. The information from each individual reporting form was processed by computer using punched cards.

The questions to be answered have been summarized in the following catalog of questions:

Question 1: On the basis of which indications was the MVA step vaccination performed?

CNS diseases	blood disease
Skin diseases, allergy	concerned parents
Chronic disease	other reason
Intestinal disease	no particular indications

[1] We want to express our appreciation to Dr. Drausnick of the Bavarian State Ministry of the Interior and the Bavarian Statistical State Office for assistance in performing the statistical analyses.

Question 2: In how many vaccinated patients was any one of the following reactions observed at the vaccination site 24 to 48 hours or 5 to 7 days after the MVA vaccination (first vaccination stage)?

No reaction
Redness up to 10 mm with infiltrate
Redness up to 10 mm without infiltrate
Redness 10–20 mm with infiltrate
Redness 10–20 mm without infiltrate
Redness more than 20 mm with infiltrate
Redness more than 20 mm without infiltrate

Question 3: How many vaccinated patients have experienced concomitant symptoms (fever more than 38°C and/or disturbance in general well-being) after the MVA vaccination (first vaccination stage)?

Question 4: How many vaccinated patients have developed any one of the following evaluations of local findings of the main epicutaneous vaccination (second vaccination stage) on the 7th day after vaccination?

Vesicles or pustules	without scabbing
Vesicles or pustules	with scabbing
Infiltrate or nodules	without scabbing
Infiltrate or nodules	with scabbing
Negative local findings	

Question 5: In how many cases did concomitant symptoms develop after the epicutaneous main vaccination (second vaccination stage) and which type of concomitant symptoms were they?

Table 1. Leading indications for MVA step vaccination.
Number of cases observed: 3850

Central venous disease	3.1%	Blood diseases	0.25%
Skin disease, allergy	8.4%	Concerned parents	23.0%
Chronic disease	2.0%	Other reason	13.9%
Intestinal disease	0.5%	No particular indication	48.4%
No information	0.4%		

Results

The results are summarized in Tables 1 through 5. The different total number of observations for the individual questions is due to the fact that many questions were not answered on all questionnaires.

So far a total of 7098 first vaccinated patients have been covered by the study. Five thousand six hundred ninety-one were less than 3 years old and 1407 were more than 3 years old.

Discussion

The conventional attempts to improve the tolerability of vaccinations have previously taken into account the condition of the vaccinated patient prior to vaccination and attempted to attenuate the systemic response to epicutaneous prophylactic vaccination through various vaccination

methods in the hopes of thereby avoiding vaccination complications.

However, with our good epidemiological situation, smallpox vaccination is aimed directly at a smallpox infection only in extremely rare cases, so the goal of the initial vaccination is to create a basal vaccination immunity so that in the serious case a low-risk repeat vaccination can be administered. In Germany, an infant or toddler will hardly come in contact with *Variola vera*. Previous experience has shown that exposure occurs in later years, however, this means that we are "vaccinating against the vaccination" [23, 24].

Attempts with vaccine antigen have not proven adequately successful because vaccine antigen merely induces a cellular allergy. The vaccine antigen is a fully virulent vaccinia virus that has been inactivated by treatment with formaldehyde. This destroys mainly the nucleoproteins. The proteins are partially denatured and the lipoproteins of the shell are preserved. However, the latter is the actual allergen. The significance of this component of the vaccinia virus is low in terms of immunization. The vaccine antigen is therefore regarded as more or less ineffective in Anglo-American and Swiss literature.

An attempt to burden an adoptive immunity induced by vaccine antigen by adding vaccinia virus or variola virus has not been successful in detecting a protective effect of the vaccine antigen [11, 19].

The efficacy of the preparation as an allergen is illustrated by allergic reactions (rash, vaccination ulcer) in an incidence of 5 to 8% in the subsequent vaccination using the original vaccinia virus.

Attenuated vaccinia virus MVA, however, has an intact nucleoprotein component. The formation of hemagglutinin has been reduced by culturing in cell passages. Only with repeated injections of MVA have low titers of hemagglutination inhibiting antibodies in the serum been detected in experimental animals.

Nevertheless, MVA is capable of building up a true anti-infectious immunity without any greater infectious allergic vaccination reaction.

Experience since the introduction of the smallpox vaccination has shown that cerebral complications almost never occur after a repeat vaccination (incidence lower than 1:2,000,000). All observed cases have so far involved such atypical findings that it is reasonable to have serious doubts that repeat vaccination encephalitis exists at all [10].

For the MVA stepwise vaccination, this means that—even in the absence of hemagglutination inhibiting antibodies—no CNS disorders need be expected if a repeat vaccination reaction is induced in a second vaccination using fully virulent vaccinia virus.

Therefore, the goal of this investigation was to ascertain to what extent the initial vaccination stage with MVA would furnish the person receiving the initial vaccination with a basal vaccination immunity, i.e., giving this person the responses of a person receiving a repeat vaccination.

The simplest proof of basal vaccination immunity is vaccination with a virulent vaccinia virus and subsequent evaluation of the vaccination reaction.

The clinical signs after a prophylactic smallpox vaccination have been well known for a long time and have been described in detail in the literature. A summary review was given recently by Herrlich [10] in the Handbook for Prophylactic Vaccinations.

We differentiate the local reaction at the vaccination site and the general systemic vaccination reaction. The local vaccination reaction shows two characteristic manifestations: the initial vaccination reaction and the repeat vaccination reaction. The initial vaccination response leads over the course of several days to formation of a pustule by way of a papule and vesicle stage. The pustule reaction has reached its peak on the 7th day after the vaccination. Then the stage of scabbing begins. The local reaction ends with the scab falling away and formation of a scar.

The repeat vaccination reaction is a reliable sign that the body has already had an immunological encounter with the virus, so this is an important criterion for the immune status and the success of previous vaccinations.

The most important difference between the initial vaccination reaction and the repeat vaccination reaction is the accelerated course. Although the repeat vaccination reaction might pass through the same morphological stages of the initial reaction, the individual stages are shortened in time, however. An important criterion that is important in evaluating the vaccination reaction on the seventh day after the vaccination is being morphological manifestation of the vaccination pustule:

Whereas the initial vaccination reaction is to form a taut pustule without any scabbing at all, the repeat vaccination reaction on the same day develops more or less completely scabbing of the pustule.

The systemic reactions are generally less pronounced in repeat vaccinations than in initial vaccinations.

The transition between the normal general vaccination reaction, which accompanies almost every smallpox vaccination, and the vaccination complication is fluid. It is often difficult to find the causal relationship with the prior smallpox vaccination in the case of uncharacteristic disorders in general well-being.

General symptoms that are often mentioned following a smallpox vaccination include: fever, fatigue, joint pain, headaches, swelling and painful local lymph nodes, transient exanthem, isolated secondary pustules or secondary efflorescences. The relative frequency with which such symptoms occur after an initial vaccination and a repeat vaccination cannot be ascertained because they are tolerated as "normal" vaccination reactions and do not get included in statistics. The observations on smaller vaccination groups with respect to such manifestations are doubtfully representative especially since they are usually based on clear-cut vaccination subjects.

In addition to these manifestations which are considered to be an abnormal vaccination response only due to their severity, there are specific vaccination complications which include, first, the disease syndromes that are recognizable as vaccination lesions of the outer integument (vaccinia generalisata, eczema vaccinatum, vaccinia ulcerosa) and secondly, the disorders of the central nervous system known collectively as post-vaccination encephalopathy and encephalitis.

The third category includes all complications not specifically caused by the vaccination disorder but clearly occurring as a result of the vaccinia infection and the predisposition thereby created. Stickl [18, 21] and other authors have pointed out the importance of these diseases in

evaluating vaccination damage. These are attributed mainly to a change in the body's reaction with lowered resistance to bacterial infections.

The evaluation of the incidence of individual complications is subject to great fluctuations. These discrepancies in the evaluation have been the subject matter of scientific discussion at all times without being able to achieve a clear-cut elucidation so far.

Safety

The information about MVA vaccination is based on 7098 initial vaccination recipients. They were divided into those less than 3 years of age and those more than 3 years of age. The second group was formed because according to the consensus so far, the third year of life is the cut-off limit for "being above age" for the first vaccination. After the third year of life, in the opinion of various authors, the incidence of cerebral complications is greater than that in younger vaccination patients [1–4, 6–9, 16].

The local reaction after initial MVA immunization is manifested as an approximately circular area of redness at the intracutaneous vaccination site with or without minor infiltration. After 24 to 48 hours, the area of redness reaches a diameter of up to 10 mm (in 54.9% of the cases), of 10–20 mm (31.45%) or in a few cases (6.4%) more than 20 mm. In 367 vaccination patients (7.25%) the local response was negative (Table 2). This may be an inadequate response of the vaccination patient but it may also be attributed to the injection of the vaccine being too deep, inadvertently subcutaneous. With a subcutaneous injection, no local reaction occurs with the dose of infectious virus specified for MVA. Nevertheless, this form of administration is without influence on the results of the reaction of the second vaccination stage.

Table 2. Local reaction after MVA vaccination (first vaccination stage)
24–48 hours and 5–7 days after vaccination (p.v.).

	24–48 hours p.v. (number of cases: 5065)	5–7 days p.v. (number of cases: 5308)
No reaction	7.25%	9.17%
Redness up to 10 mm	54.90%	75.45%
Redness 10–20 mm	31.45%	14.05%
Redness more than 20 mm	6.40%	1.53%

Seven days after the MVA vaccination, the local findings according to type and extent are weaker than after 24 to 48 hours. The distribution among the categories "negative," "up to 10 mm," "10–20 mm" and "more than 20 mm" changes on the fifth to seventh day in favor of the weaker reactions, namely the negative reactions increase from 7.25% to 9.17%, the reactions with a diameter of up to 10 mm increases from 56.61% to 75.45%. However, the reactions with a diameter of 10 to 20 mm decreases from 30.61% to 14.05% and those with a diameter of more than 20 mm decrease from 4.82% to 1.53%.

It seems especially worth mentioning except for redness and infiltration, no more extensive reactions at the vaccination site were observed: no vesicles or pustules and no ulcerations. Not even minor scabbing of the injection site has been reported. This is important because a classical cutaneous vaccination reaction can also be expected with the low local infection dose of 2×10^5 infectious virus particles when using conventional Vaccinia strains. A review article by Dostal [5] shows that a conventional strain with a virus content of approximately 10^6 infectious particles/mL, corresponding to the virus content of MVA vaccine, causes the vaccination to "take," i.e., causes a pustule reaction, in 50% of all first vaccinations. We can conclude from this comparison that the skin virulence of the MVA strain is greatly reduced in humans in comparison with conventional vaccinia strains. The reduced skin virulence has also been demonstrated in animal experiments by Mayr and Munz [14] and by Hochstein-Mintzel et al. [12] on the rabbit and monkey.

The local reaction after MVA vaccination has thus proven to be without a doubt milder than the reaction after conventional prophylactic vaccination. Consequently, none of the complications that are expected with prophylactic smallpox vaccinations involving the skin as an organ, including vaccinia generalisata and eczema vaccinatum, occur with MVA vaccination. Furthermore, MVA virus can be expected to cause no complications that are secondarily attributable to destruction of epidermal structures. We should think here primarily of post-vaccination encephalitis, the development of which is to be explained presumably in conjunction with the phylogenetic bridges between the skin and brain and the antigen relationships to be expected with this [22].

In most cases no general reaction has occurred after MVA vaccination. Only 2.28% of the patients vaccinated have developed fever and 4.11% reported a disturbance in general well-being. With the incidence with which fever and a disturbance in general well-being occur in children normally anyway, not all the observed cases will have to be causally attributable to the vaccination. Even if all observed febrile courses are attributed to the MVA vaccination, a febrile vaccination response of only 2.28% of all children receiving vaccinations may be considered minor (Table 3).

Table 3. Concomitant symptoms after MVA vaccination (first vaccination stage).
Number of cases observed: 7098.

Fever above 38°C	2.28%
Disturbance in general well-being	4.11%

The tolerability of the vaccination method is thus documented by Tables 2 and 3. In addition to the 7098 individually analyzed cases, there are numerous general reports of vaccinations proceeding without any complications. In view of the fact that any serious complication would have to be reported immediately, this greatly increases the empirical relevance of our study.

Efficacy

The classical proof of efficacy of prophylactic vaccination is an increase in hemagglutination-inhibiting or virus neutralizing antibodies, but this proof cannot be obtained for a single MVA vaccination alone. This had already been demonstrated in animal experiments [12] and in

humans [20]. An increase in the level of antibodies can be detected only by administering two MVA vaccinations with high virus doses. However, antiviral immunity is determined not exclusively by humoral defense mechanisms but also by cellular defense mechanisms, the details of which are not understood.

This can be demonstrated by indirect evidence, namely when an anti-infectious immunity is observed clinically but no serologic antibodies can be detected. In animal experiments, it has been observed that after MVA vaccination, there has been increased resistance to the stress or infections with variola virus although there was no serological evidence of antibodies in these animals [13].

The classical proof of the changes in tissue reactivity of a person having vaccinia immunity is the accelerated course of a vaccination reaction on receiving a repeat vaccination. The definitely different manifestations of initial vaccination reaction and repeat vaccination reaction have already been pointed out in the discussion.

In our field study, the cutaneous vaccination reaction type after a conventional smallpox vaccination became the parameter of efficacy of an MVA vaccination: if the cutaneous vaccination is accelerated when administered after an MVA vaccination, i.e., if it proceeds as a repeat vaccination reaction, then the MVA vaccination must have induced an immunization (sensitization). If the conventional cutaneous smallpox vaccination after MVA vaccination proceeds without any signs of influence, then the MVA vaccination would be of no effect.

Proof of the immunogenic efficacy of MVA in animal experiments had already been obtained prior to the clinical trial. Animals of various species were to be immunized against an infectious burden with vaccinia virus as well as against an infectious burden with variola virus. The efficacy was essentially a question of immunization dose, whereby assuming the same dose the Elstree strain was more effective than the MVA strain [12].

Table 4 summarizes the observations on humans regarding the cutaneous vaccination reaction following MVA vaccination. The classification criteria were selected so that they did not have to allow a clear differentiation of reaction types. At the same time, they should allow a classification of the vaccination reactions according to the classification proposal of the World Health Organization and ultimately should help in objectifying the question of the evaluation as "first" or "repeat vaccination reaction."

Table 4. Local reaction after epicutaneous vaccination with dermovirus Elstree strain
(second vaccination stage) on day 7 after vaccination.
Number of cases observed: 6894.

Vesicles or pustules without scabbing	18.10%
Vesicles or pustules with scabbing	47.65%
Infiltrate or nodules with scabbing	18.51%
Infiltrate or nodules without scabbing	8.69%
Negative local findings	7.05%

Assuming that the classical initial vaccination reaction is characterized by a pustule without scabbing on the seventh day after vaccination, then Table 4 shows that this requirement is met in only 18.1% of the cases. The reported objective findings at the vaccination site thus yielded only 18.1% traditional initial vaccination reactions although 100% was expected because there were exclusively initial vaccination patients. The percentage of negative reactions (7%) ascertained in this group is unusually high for patients receiving an initial vaccination. The observed percentage is reminiscent of numbers that would be expected for repeat vaccinations.

The difficulty with the smallpox vaccination "taking" after an MVA vaccination has also been expressed in numerous reports and inquiries from colleagues by telephone.

If we assume the nodule reaction without scabbing in the sense of the WHO classification to be a reaction with questionable vaccination success, this yields the following distribution of reactions:

Vaccinations total	6894 (100%)
of these, successful	
in the sense of an initial vaccination reaction	1248 (18.1%)
in the sense of a repeat vaccination reaction	4561 (66.16%)
positive (major reaction)	5809 (84.26%)
questionable (equivocal reaction)	599 (8.69%)
negative	486 (7.05%)

The distribution of reaction types according to main cutaneous vaccination is approximately the same with all types of local MVA reaction. Even with negative local findings after MVA vaccination, initial vaccination reactions after cutaneous main vaccination are no more common than after strong local reactions. This suggests that intracutaneous administration and local signs of irritation of the skin are not a condition for successful immunization.

Animal experiments have also shown that immunization against pox is possible, bypassing the skin. Rabbits and monkeys have been successfully immunized against vaccinia and variola by administering the vaccine intramuscularly [13]. These experimental findings and the results of clinical testing might allow the conclusion that the interfering local vaccination reaction should be eliminated in MVA vaccination and the vaccine should be administered subcutaneously, intramuscularly, orally or in the form of an aerosol.

The efficacy of the MVA vaccination in addition to the local vaccination reaction, the incidence of fever and other disturbances in general well-being after cutaneous main vaccination was interpreted as the second criterion. Reliable numbers regarding the incidence of fever with conventional initial vaccination of healthy children are difficult to obtain. In general terms, however, it can be concluded that the so-called vaccination fever is a "normal" concomitant reaction to a smallpox vaccination. In our study, fever was reported in 18.39% of 5982 cases analyzed. The majority (58.87%) of the vaccinated children having a febrile reaction course, broken down according to extent of fever and duration of fever, had a temperature rise of only up to 38.5°C for less than 2 days. A greater increase in temperature for a shorter or longer period of time (22.49% and 11.24% for less than 2 days and more than 2 days, respectively) were far less common; likewise the longer persistence of lower temperatures (7.40%).

The other concomitant systems after cutaneous main vaccination were of a harmless nature and are not observed in this frequency with repeat vaccinations (Table 5).

Table 5. Incidence of concomitant symptoms after epicutaneous vaccination with

Elstree strain dermovirus (second vaccination stage). Number of cases observed: 5691.

Nausea/vomiting	0.78%
Cerebral symptoms	– *
Febrile convulsion	– *
Rash	0.78%
Lymph node swelling	3.82%
"Other"	2.60%

*In an earlier publication [17], three neurological symptoms were listed. A follow-up of these cases has revealed that there was no correlation with the smallpox vaccination.

No CNS complications of the vaccination were observed. However, since the number of cases observed here is too small, a final conclusion regarding the incidence of encephalitis cannot yet be made.

The morphological course of the MVA stepwise vaccination with "nodule reaction," accelerated scabbing reaction shows that the second vaccination stage usually proceeds as a repeat vaccination reaction in the essential biological immunological criteria. Therefore, the contraindications of an MVA stepwise vaccination would be equivalent to those for a repeat vaccination.

One difficulty with the MVA stepwise vaccination should be pointed out: it is often impossible to clarify whether a bland accelerated scabbing reaction can be interpreted as a sign of adequate vaccination success. In case of doubt, a revaccination should always be performed after a few months or the success of the vaccination should be confirmed by the neutralization test.

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EXHIBIT 7

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

BAVARIAN NORDIC A/S, and ANTON MAYR,	)	
Plaintiffs,	)	Civil Action No.
V.	)	05-614 (SLR)
ACAMBIS INC. and ACAMBIS, PLC,	)	
Defendants.	)	

Deposition of PROF. DR. DRES. H.C. JOSEPH STRAUS

Washington, DC

Thursday, November 30, 2006

JOB NO. 177837

PAGES 1-125

Reported by: Denise Vickery, RMR-CRR

November 30, 2006
10:07 a.m.

Deposition of PROF. DR. DRES. H.C. JOSEPH STRAUS, held at the offices of:

BINGHAM McCUTCHEN LLP
The Washington Harbour
3000 K Street NW, Suite 300
Washington, DC 20007-5116

Pursuant to notice, before Denise Dobner Vickery, a Registered Merit Reporter, Notary Public of the District of Columbia.

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I N D E X

Exhibits attached.

(Thereupon, a document was marked for identification Exhibit Nos. 1 through 3.)
Thereupon,
PROF. DR. DRES. H.C. JOSEPH STRAUS
was called for examination, and, after having been duly sworn or affirmed, was examined and testified as follows:

EXAMINATION BY COUNSEL FOR THE DEFENDANTS
BY MR. DUNN:

Q. Good morning, Professor. Would you please state your full legal name?
A. My full legal name is Joseph Johannes Ricardos Straus.
Q. And where do you reside, sir?
A. I reside in Munich.
Q. Could I have your home residence address?
A. Franz Reber 7. Franz, F-r-a-n-zet, Reber, R-e-b-e-r, number 7.
Q. And you are a citizen of what country, sir?
A. Italy.
Q. Italy?
A. Yes.

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or not?
A. I took all the exams at the university and no further.
Q. Was there then an additional exam that would have been required had you been a Yugoslavian citizen in order to be admitted to practice law in Yugoslavia?
A. That is correct.
Q. And you did not sit for that exam?
A. No.
Q. What was your next legal training?
A. I was awarded a scholarship of the Bavarian Ministry For Education, and I took the legal training at the University of Munich, meaning that I got training in German public and private law and I took the exams and got a certificate that I am in command of that law.
Q. Okay. Let's break that down a little bit. This is at the which university?
A. Of Munich.
Q. Of Munich?
A. Yes.
Q. Okay. So what classes did you take that were

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specific to German civil law?
A. Well, we had Professor Grauer's class on German civil law.
Q. Okay. How many -- is that one course?
A. Well, two semesters.
Q. Okay. One two-semester course --
A. Yes.
Q. -- on civil law?
A. On civil law, yes.
Q. What courses did you take at University of Munich that were specific to German property law?
A. That covered also the German property law. It's a special course taught at that time and I think also today of foreign law students who enroll in the German universities.
Q. So, even though you were doing graduate studies, this was a course that was designed I gather to substitute for what a German law student would have received as part of his basic law school training?
A. I would say an intermediary. It's like an LLM course here because that was a precondition to be admitted as a student for Ph.D.

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Q. Okay. Other than for that one two-semester course, what other courses have you had from the University of Munich that were specific to German civil law or German property law?
A. I think the civil procedure but no additional courses on specifically property.
Q. And when did you then graduate from the University of Munich?
A. Well, first I received that certificate in 1964 because that was between 1963 and '64, and then I received my Ph.D. degree in 1968 and for that degree, I had to pass also an oral examination in German public and private law. And one of my examiners in that Rigorosum what is called was Professor Lawrence who was the leading authority in civil law in Germany.
Q. Okay. But so that we're clear, for your basic legal training that you had in Yugoslavia, you had no courses dealing with German civil or property law?
A. As I said.
Q. Then when you came to the University of Munich to begin working on your postgraduate doctorate degree?
A. Yes.

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Q. You had one two-semester course that was specific to German civil law?
A. Exactly.
Q. You then obtained your Ph.D. in 1968?
A. Yes.
Q. Now, you also -- do you also hold a professorship at the University of Munich?
A. Yes. Honorary professor.
Q. Pardon?
A. It's a very special figure.
Q. I didn't hear what you said. Could you just repeat what you said?
A. Honorary professorship.
Q. Honorary professorship?
A. Well, yes.
Q. Is that how you describe it in paragraph 3 of your report, Exhibit 1?
A. That I am a professor of law at the Universities of Munich and Ljubljana.
Q. Have you disclosed in your qualifications here in your report that it's an honorary professorship?
A. It's on this page of the bibliography.

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Q. The bibliography --
A. Yes.
Q. -- that was just handed to me this morning?
A. Yes.
Q. I'm talking about your expert report now, sir. In the qualification section, do you disclose that this is an honorary professorship?
A. If I may, I have to describe what does it mean, an honorary professorship.
Q. I'll give you that opportunity in a second.
A. Yes.
Q. First of all, have you described it as being an honorary professorship?
A. No, I didn't.
Q. Okay. What is -- first off, in German -- in Germany at the university, are there various levels of professorship?
MR. PENNINGTON: Objection, vague and relevance.
BY MR. DUNN:
Q. That's for the record. You can now answer.
A. They are -- there are full professors and

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associate professors, but they don't -- you don't see that in a title.
Q. Are you a full professor?
A. I am not a full professor.
Q. Are you an associate professor?
A. I am not an associate professor.
Q. This is an honorary professorship?
A. This is an honorary professorship in terms of German law.
Q. Okay. And have you ever written a postdoctoral thesis on German law?
MR. PENNINGTON: Objection, foundation vague.
THE WITNESS: What do you understand a postdoctoral thesis?
BY MR. DUNN:
Q. Did you -- for purposes of obtaining your doctorate, did you have to write a thesis?
A. Yes.
Q. Was it specific to German law?
A. It was a comparative thesis on German and Yugoslav law in unfair competition.

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Q. Unfair competition?
A. Yes.
Q. Did not deal with German civil property law?
A. No.
Q. Have you ever received the status of what I understand is referred to as habilitation from a German university?
A. Not from a German university.
Q. Am I correct that your honorary professorship allows you to lecture in the field of patent and intellectual patent law?
A. Yes.
Q. Have you ever conducted lectures at the German university that were specific to German civil law?
A. No.
Q. Or that were specific to German property law as distinct from intellectual property?
A. Not lectures.
Q. Now, after you got your doctorate in 1968, I understand that you then went into private practice; is that correct?
A. Yes.

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Q. What was your first job after obtaining your doctorate?
A. I was an associate with the law office being in Munich, having a part in New York and part in Tel Aviv.
Q. Was that the Nath firm?
A. Yes, exactly.
Q. So you were an associate?
A. Well, I was in charge of dealing with restitution claims and that I started already before I graduated. I had to make my living after, yes.
Q. And what do you mean by restitution claims?
A. Oh, the Nazi claims as against the Federal Republic of Germany. Claims of prosecuted Jewish -- especially Jewish victims of Nazis.
Q. Okay. And you were doing this before you got your Ph.D.?
A. In part because I had to make my living from a certain point in time when my scholarship of the Bavarian Ministry of Education lapsed.
Q. Am I correct that this then did not require you to be admitted to practice law before any German

court?
A. That's exactly correct, yes.
Q. And at the time that you were working for the Nath firm in Munich, am I correct that you were not admitted to practice law before a German court?
A. That's correct, and I was an Italian citizen all the time.
Q. Have you ever been admitted to practice law in Italy?
A. No.
Q. What was the next position that you held as far as employment after the Nath firm?
A. Well, I made the so-called scientific area at the Max Planck Institute starting with being a so-called scientific collaborator. Then I became head of department.
Q. Hold that thought and we'll come to Max Planck in a minute.
A. Yes.
Q. I thought that you also worked with the Rozenberg firm?
A. This was a collaboration. Rozenberg,

Kestenberg and Nath.
Q. Okay. So from -- am I correct that from 1968 to 1977, you were engaged in this restitution work?
A. Yes.
Q. For a collaborative group of law firms; the Nath, the Rozenberg firm in Tel Aviv, and the Kestenberg firm in New York?
A. Yes.
Q. Did the nature of your work during those years from 1968 to 1977 change?
MR. PENNINGTON: Objection, vague.
THE WITNESS: What does it mean changed?
BY MR. DUNN:
Q. Well, would the nature of your duties -- did the nature of your duties change significantly during that time period, or were you doing the same thing pretty much for that entire time period?
A. Well, it's changed in the sense that I have had both more and more experience, more responsibilities to negotiate with Senator Javits. I corresponded with Vice President Spiro Agnew in the case of the Jews prosecuted from Greece, which were not

really entirely well treated in the entire. So we made the settlement. So that is -- that is the change of responsibilities. Maybe not the legal terms, but it's what the work was at hand.
Q. But the nature of the work continued to be relating to restitution claims?
A. Yes, that's correct.
Q. And the nature -- your status did not change during that time period as far as, for example, becoming admitted to practice law in Germany?
A. No, it didn't.
Q. So throughout that time period from 1968 to 1977, you were not admitted to practice law?
A. That's correct.
Q. Okay. The next position that you held I believe you said was when you went to the Max Planck Institute?
A. I should clarify that I made my Ph.D. at the University of Munich and I was at the Max Planck Institute.
Q. Okay.
A. So I returned practically as a full position

back to the Max Planck Institute.
Q. And what was your entry -- strike that.
When you came back to the Max Planck Institute in 1977, what was your initial --
A. '74 as I said before, yes.
Q. I'm sorry. In 1974 when you came back to Max Planck Institute, what was your initial position at that time?
A. Scientific collaborator. Wissenschaftlicher Mitarbeiter. That's the only position you can have before you become actually head of department or director.
Q. Okay. Scientific collaborator. What did you do?
A. It depends.
MR. PENNINGTON: Objection, vague.
MR. DUNN: Hmm?
MR. PENNINGTON: Objection, vague.
BY MR. DUNN:
Q. Describe your duties.
A. You can be a scientific collaborator dealing with American law.

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Q. Excuse me, sir. I want to know what you did.
A. My -- my own, I was involved in unfair competition, patent law and whatever was at hand with the former, I'd say, Eastern European law.
Q. Okay. Since 1977, have you taught any courses that were specific to German civil law?
A. No.
Q. Have you taught any courses that were specific to German personal property?
A. No.
Q. If you refer to Exhibit Number 1 and your qualifications, you note that you: "Beginning in 1989, I have been a visiting professor of law at Cornell Law School, Ithaca, New York."
A. Yes.
Q. Do you see that?
A. Yes.
Q. Sir, I went and checked the Cornell Law School Web site and your name doesn't appear. Can you explain that?
A. I can show you a number of directories of the Cornell Law School where you can find my name.

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Q. When was the last time that you were a visiting professor of law at Cornell University?
A. '98.
Q. 1998?
A. Yes.
Q. So, when you say "Beginning in 1989, I have been a visiting professor of law at Cornell Law School," you left off the fact that that stopped as of 1998?
A. Yeah.
Q. Bavarian Nordic counsel has handed me what's been described before we went on the record as an updated or corrected bibliography of yours, which I'll hand you, which has been marked as Straus Exhibit Number 3. Can you identify for me any publications that you have authored that are specific to German civil law?
MR. PENNINGTON: Let me state an objection for the record that the document is quite numerous, and I'll state an objection as to foundation with respect to what the German civil law is.
BY MR. DUNN:

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Q. His objections are for the record. You can answer.
A. Well, that's the monograph published with Dr. Moufang on the, in English, "Deposit and Release of Biological Material."
Q. And what number would that be on this exhibit?
A. Number 5.
Q. Number 5. And you say that that is specific to German civil law?
A. Not entirely specific, but it deals with questions of property of German civil law.
Q. Okay. Out of the approximately other 335 publications that are listed here, are there any other publications that you can identify that you consider to be specific to German civil law?
A. I don't believe.
Q. I'm not going to mark this because it's on a loan, but the one publication that you're referring to is, as I understand it, this book "Deposit and Release of Biological Material For the Purpose of Patent Procedure: Industrial and Tangible Property Issues"?
A. Yes.

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Q. Are you familiar with the procedures that are to be followed if one does wish to become qualified to practice law before a German civil court?
A. Yes.
Q. Am I correct that you would first need four years of university, followed by the first state examination in order to become what's known as a jurist?
A. That's correct.
Q. That you would then need an internship known I believe as Referendar followed by a second state examination?
A. That's correct.
Q. And if you successfully complete that, you would have the status of assessor, or Volljurist?
A. That's correct.
Q. After then you would then be eligible to be admitted to the bar as an attorney of law?
A. Yes.
Q. And that in Germany you can only act as an independent legal advisor after passing both the first and second state exams and then being admitted to the

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be a supplemental report coming out for the deposition the next day. I consider that improper.

MR. PENNINGTON: Okay. I'll state for the record that I don't believe the supplemental report was prepared and signed until it was just about at the time that it was sent out. I was not responsible for sending it out, but I believe we sent it out in the normal fashion that everybody has used in this case.

And as far as common courtesy, I'll state for the record, too, that you are, have been and continue to be one of the rudest attorneys I've ever worked with in terms of dealing with -- with foreign witnesses who, for example, do not have English as their primary language. You continue to be short with the witness.

You continue to ask questions in a hostile manner. Even though this witness is not being hostile. And I think as long as you're talking about manners and courtesy, I believe you're lacking those in how you handle witnesses.

MR. DUNN: Be glad to have any court review behaviors here.

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BY MR. DUNN:

Q. Sir, let's get back to your testimony. In the interim between your first report, Exhibit 1, and your supplemental report, Exhibit 2, had German law changed at all?

A. No.

Q. Had the facts relevant to your opinions changed at all?

A. The only -- the facts have not changed, but I have to add, if I may, that I visited Professor Mayr and had a short talk with him.

Q. When did you visit with Professor Mayr?

A. Last week on Monday.

Q. At whose suggestion was that?

A. The in-house counsel, if I'm correct in my English expression, of Bavarian Nordic.

Q. Are you referring to Dr. Westerlund?

A. I refer to her, yes, yes.

Q. Did Dr. Westerlund accompany you?

A. Yes, she did. Not accompany. She was there. When I came, she was there also with Mr. or Professor Mayr.

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Q. And who else was present?

A. His wife.

Q. Anyone else?

A. No.

Q. Did you take any notes of your meeting?

A. Actually, no.

Q. Did Dr. Westerlund take any notes of the meeting?

A. I don't believe so.

Q. Was it recorded in any way?

A. No.

Q. What were you told as far as the reason for the meeting?

A. That I should see him in order to get personal impression of the gentleman, who is now 80 and around that -- I don't know what his age exactly is -- and also to have an opportunity maybe to ask one or the other question, especially as far as his general way of dealing in, I'd say, how to serve and how to cooperate with his colleagues.

Q. Do you make any reference to this meeting with Professor Mayr in your supplemental report?

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A. No.

Q. Do you make any reference to it as being additional material that you have reviewed or relied upon?

A. No.

Q. In any of your reports, have you discussed --

A. The only -- the only additional document to which I refer is the report of Professor Tilmann.

Q. Okay. Well, tell me about your meeting with Professor Mayr.

A. Well, I just wanted to see him and to hear how he has been handling, let's say, sending samples to other colleagues and also maybe to the industry.

Q. And why did you want this information?

A. It's always good -- I've learned from Mr. Rozenberg, it's always good to see people to know how to, let's say, estimate them.

Q. Well, what additional information did you expect or hope to be able to obtain from Professor Mayr that you had not already been able to ascertain from your review of the materials?

MR. PENNINGTON: Objection, foundation

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and vague.
THE WITNESS: I had, let's say, not -- I was not able to get from neither his deposition, which I of course under the time pressure read it, but there were no -- there was no information of how he handled maybe his relationship with industry.
BY MR. DUNN:
Q. Okay. What questions did you ask him?
A. Well, whether or not he sent materials to companies and if under which conditions, and I should add that, of course, I was not there as deposing Professor Mayr, but as a friendly colleague of him to find out what his attitude is. So it was not a question, have you, did you. So I wasn't and didn't ask. His answer was he actually sent samples also to companies, and it has always been understood that he didn't make any limitations in writing or whatever, but it was understood that after testing, they would negotiate whether or not it would be transfer ownership or whatever licensing agreement. That was new to me and I -- at least to me. Maybe not to others but to me.

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Q. He told you -- if I understood your testimony correctly, he told you that it had been his common practice to send out biological samples without there being any written expression of any restriction?
A. I would be careful to use the word common practice, but he named companies like Bayer, if I'm correct. That was one of the leading -- still they are, but not owned any more by Hearst. That he had that kind of a relationship to send them, and then only afterwards to negotiate a question of whether or not something will follow, and that it was understood that without that second, whatever it is, no rights were transferred to those companies.
Q. Let's try to separate out what he may have subjectively understood versus what was objectively stated or put in writing. What I'd like to know is: Did he confirm for you that he had frequently sent out biological samples without there being any written statement placing in writing a restriction on the use of the materials?
MR. PENNINGTON: Objection, vague.
THE WITNESS: I would carefully phrase

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that I understood his statement that in the cases where there was some relationship with certain company, that that was the case. That he didn't ask -- didn't impose any written limitations, and it was commonly understood that he was still in control of -- of the ownership.
BY MR. DUNN:
Q. Commonly understood by Dr. Mayr is what he told you?
A. Well, if --
MR. PENNINGTON: Objection, mischaracterizes the testimony.
THE WITNESS: As I understood him.
BY MR. DUNN:
Q. Did you do any investigation to see whether that understanding had also been the understanding of the recipient?
A. I had no opportunity to do that.
Q. Okay.
A. I had no reason to do that.
Q. What else did you discuss with Dr. Mayr or Professor Mayr?

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A. Well, a little bit of his theory. What in which function he was where and as far as his memory was still okay what he did in Munich and Tuebingen and back in Munich and what was his position at a certain point in time.
Q. And how long did all this take, your discussions your meeting?
A. Difficult to say, but maybe two hours, something like that.
Q. What did he tell you about his work history?
A. Well, mainly what he did, meaning that he was involved in the vaccine business. That he was first with the Bavarian Vaccine.
Q. Vaccine Institute?
A. -- Institute and that he became -- I don't know what his first position was in Tuebingen, but again he was the boss in Tuebingen.
Q. But that it all started at the Vaccine Institute?
A. That the --
MR. PENNINGTON: Objection, vague and foundation.

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foundation.
THE WITNESS: Question of existence wouldn't be decided, at least not in Europe. It would be decided whether or not it was made publicly available or not before date of filing of priority.
BY MR. DUNN:
Q. Are you aware of any patents covering passage 572 of MVA virus that was created in 1974?
A. No.
Q. Is it your opinion, sir -- or strike that.
Do you consider yourself an expert on choice of law questions what law governs?
A. One has always to be cautious in calling somebody an expert. I usually say a so-called expert. I wrote an article in which I have actually influenced the case law and doctrine on the choice of law or not as far as employees inventions are at hand, but in general I would say I possess of some skills in international private law, conflicts of law. If law says you could have as defined, but colleague being an expert of choice of law, I wouldn't say that.
Q. Have you attempted to do any research that is

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specific to what the appropriate choice of law would be for a federal court sitting in Delaware with regard to these facts?
MR. PENNINGTON: Objection, vague.
THE WITNESS: I haven't thought that.
BY MR. DUNN:
Q. And so you -- just so that we're clear, you're not sitting here today purporting to express an expert opinion as to what the judge in this case in Delaware should decide as far as choice of law principles?
A. I haven't thought through that.
Q. Okay. And you haven't expressed an opinion on that?
A. No. But as I stated before, in the Pfizer case was a question. So, that's...
Q. I am --
A. This correct. I haven't thought that and I didn't investigate it.
Q. In this case?
A. Yes. No.
Q. So, am I correct in interpreting your report and the opinions that you have expressed as far as

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German law that these are opinions that you are offering to the assistance of the US court in the event that the US court determines that German law applies?
MR. PENNINGTON: Objection, vague.
THE WITNESS: Correct.
BY MR. DUNN:
Q. Now, similarly, we're dealing with and you discuss in your report transactions between MVA strain 572 that was purportedly sent from Germany to the NIH as one transaction, and then we have a subsequent transaction where other viral material made from strain 572 was sent by the NIH to Acambis and others. You're aware of that being kind of two different transactions?
A. Yes.
Q. Are you offering any opinion as to whether or not German law applies as a matter of choice of law to the transaction between NIH and Acambis?
A. Only to the extent that the material transferred from NIH to Acambis might have been not modified or not substantially modified what has been sent from Professor Mayr to Dr. Moss.
Q. I'll try to approach it a different way. Am

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I correct that you have not analyzed choice of law principles as to whether or not US law or German law would apply to a transfer of material that went from the NIH in Maryland to Acambis in Massachusetts?
A. I didn't investigate it.
Q. Turning to Exhibit 1, your first report, beginning at approximately paragraph 13, you have kind of a summary of some of the facts as you understand them that may be pertinent to your opinions.
My question for you is: How did you obtain your understanding of these facts as you've set forth in your report?
A. Well, it's certainly a combination of reading the referred publications and what I've learned from the deposition of Professor Mayr.
Q. Are these your words? Did you write this?
A. Yes.
Q. All of it?
A. I would say yes.
Q. Did you copy it from anything?
A. No.
Q. As a professor dealing with students, I'm sure

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be viewed objectively as of the time of the transfer?
MR. PENNINGTON: Objection, vague.
THE WITNESS: I would agree, yes.
BY MR. DUNN:
Q. So, referring, for example, to paragraph 23 of your first report and since the transfer that is at issue here occurred in 2001?
A. Yes.
Q. Any agreements that occurred after 2001 between Professor Mayr and Bavarian Nordic would not affect whether that 2001 transfer had in fact been a transfer of ownership?
MR. PENNINGTON: Objection, vague.
THE WITNESS: I would agree with that. Would have only an effect on BN and Mayr maybe.
BY MR. DUNN:
Q. Now, there you also reference certain agreements that were -- that predated the 2001 transfer and you reference a 1996 agreement and a 1999 agreement. I'll represent to you, sir, that the term -- by the terms of the 1999 agreement, it would have expired prior to the transfer of the MVA to Dr. Moss.

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My question to you, sir, is: Do you have any knowledge or any facts that you can point me to as to whether or not another agreement had already been put in place prior to that transfer?
MR. PENNINGTON: Objection, vague.
THE WITNESS: When I went through all the agreements and I found no lag in between dates, dates of effectiveness of the agreements were actually covering the entire period of time.
BY MR. DUNN:
Q. I'm going to try to do this generally and see if we can reach agreement. I'll represent to you, sir, that there have -- that there are documents indicating that there are still negotiations going on between Bavarian Nordic and Professor Mayr for the extension or to put in place a third agreement that were taking place during that summer of 2001.
Do you have any knowledge as to whether or not the transfer of the MVA 572 occurred while there was a lapse in those agreements and before the next agreement was put in place dating it back to an earlier time frame?

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A. To my best recollection, the entire time is covered and I don't know to what you actually refer in the negotiation. I have no knowledge about that. That dating back or not is -- is not during the period of the transfer, if at all.
Q. Let me try to handle it another way to see if we can short-circuit some of this. Assuming that there were an agreement in place between Professor Mayr and Bavarian Nordic that provided sole and exclusive access to MVA stocks in the possession of Professor Mayr, but that he nonetheless took MVA and transferred it to Dr. Moss, would that affect the legality of whether in fact there had been a transfer of ownership to Dr. Moss, or would that simply affect whether there had been a breach of an agreement between Professor Mayr and Bavarian Nordic?
MR. PENNINGTON: Objection, vague.
THE WITNESS: You're asking a hypothetical question and the answer is clear. If Professor Mayr was the owner and to my understanding he was the owner, this is the only relevant circumstance. That's the only fact.

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BY MR. DUNN:
Q. So --
A. Other things are not relevant.
Q. So we can agree that even if there was an agreement in place between Professor Mayr and Bavarian Nordic to give them access to stocks that Professor Mayr owned, that so long as Professor Mayr is assumed to be the owner of the MVA, he has it within his legal power to transfer ownership to someone else?
A. First of all, exclusive access is not ownership and he would be in a position to transfer it.
Q. Okay. So, would you agree with me, sir, that these access agreements, exclusive and sole access agreements that you refer to in paragraph 23 as having been in effect between Professor Mayr and Bavarian Nordic are irrelevant to the analysis of whether or not Professor Mayr in fact transferred ownership of a particular strain that was sent to Dr. Moss?
A. I would certainly disagree with that because I didn't by heart mention all those agreements. Those agreements clearly agree that Professor Mayr had no will to transfer the ownership.

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Q. My question is not directed towards what his will or motivation was. Am I correct that the agreements that you refer to in paragraph 23 do not change the legal power that Professor Mayr would have had as the owner of the strain to transfer ownership if he chose to?

MR. PENNINGTON: Objection, vague and foundation.

THE WITNESS: That's correct.

MR. PENNINGTON: Jeff, at some point did you want to take a lunch break?

MR. DUNN: Let's go off the record for a second.

(Recess 12:22 p.m. to 12:32 p.m.)

BY MR. DUNN:

Q. Professor Straus, I want to try to ask you some questions about the actual written communications between Professor Mayr and Dr. Moss. I'm going try to do it just generally to see if we can reach agreement and cut some of this short.

You have looked at and have reviewed the written correspondence between Professor Mayr and Dr.

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Moss, correct?

A. Yes.

Q. And will you agree with me that in none of the communications between Professor Mayr and Dr. Moss did Professor Mayr expressly state in writing any restriction on use of the strain that was being sent to Dr. Moss?

MR. PENNINGTON: Objection, vague and foundation.

THE WITNESS: I haven't seen any.

BY MR. DUNN:

Q. Are you aware of any evidence of there having been any express oral communication between Professor Mayr and Dr. Moss in which Professor Mayr verbally made an express limitation on the use of the strain that was being sent to Dr. Moss?

A. Not at the time of the exchange. Later on he expressed his view on that.

Q. You're referring now to later --

A. Yes.

Q. -- letters that may have addressed --

A. But not -- not before, as I stated.

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Q. So, just so we're clear on the record, you're not aware of any evidence of any contemporaneous oral communication between Professor Mayr and Dr. Moss in which Professor Mayr made an express limitation on the use of the strain that was being sent to Dr. Moss?

A. As I stated twice, no.

Q. Let's see if we can talk generally about the extraction principle that you and Professor Tilmann have each discussed in your reports. Okay?

A. Indirectly discussed.

Q. Can you give me an example of a situation where let's assume there has been a valid transfer of ownership. Possession and an agreement to the transfer of ownership. That has occurred.

Under that circumstance, can you give me an example of what would constitute a separate agreement that would be governed by this abstraction principle of German law?

A. Can you repeat the question?

Q. Sure. As I understand it, under German law, there is what's known as an abstraction principle?

A. Yes.

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Q. In which you would separately analyze whether there has been a transfer of ownership from whether or not there is some other agreement that may specify terms and conditions, and that under the first analysis, you look at whether there is transfer of ownership that requires change of possession and an agreement to transfer ownership. And if that has occurred, then any other agreement is analyzed separately under this abstraction principle. Is that an accurate statement?

A. That's an accurate statement, yes.

Q. And so let's take that as a hypothetical that ownership has transferred, and let's assume that there is some other agreement between the transferor and transferee. Under that set of principles or that set of assumptions where ownership has transferred, but we have a separate agreement, am I correct that breach of that separate agreement by either party does not change the fact that ownership has transferred?

A. In principle, that's correct. And the question was hypothetical.

Q. Right. I'm just trying to illustrate --

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A. I'm just trying to clarify that, yes.
Q. -- pure principles -- one at a time.
A. Okay.
Q. In the interest of trying to shorten the deposition, I'm trying to see if we can reach agreement on what I'll call pure principles of law rather than getting into application of law to facts and that's what I'm trying to do with that hypothetical. And I think we're communicating, are we not?
A. I think so.
Q. Turning to your supplemental report, Exhibit 2, if I can find it. You state at paragraph 8 on page 4. You have a quote in paragraph 8.
A. Yes.
Q. You state, quoting: "The owner of the thing delivered" -- excuse me -- "The owner of the thing deliver it to the acquirer and that both agree that the ownership is transferred, it suffices on the will of the transfer -- for the transfer of ownership is revealed from the circumstances." Let me stop there.
By that quote, you would agree that in analyzing whether there has been an agreement for

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transfer of ownership, it need not be explicit, it can be implicit from the circumstances as a legal principle?
A. I agree.
Q. Then you go on and you continue the quote, the passage that you're quoting and you say: "Whether the will to agree exists is to be judged according to the general principles applicable to the interpretation of legal transactions." You see that?
A. Yes.
Q. Now, would you agree that one of the other general principles of German law is that it should be judged objectively?
A. There are different theories on this question. Whether it should be --
Q. I don't mean to cut you off, but just so we're clear, I want your understanding of German law, not the theories. I want to know what the German law is.
A. Objectively in the sense that you have to take into account the understanding of the receiver, recipient in the context. Otherwise, you cannot have an objective assessment of that.

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Q. Okay. So you have to objectively take into account how it would be viewed by the recipient?
A. Also by the recipient.
Q. Okay.
A. By both.
Q. Paragraph 33 of your first report, the end of the paragraph you make reference to Therion Biologics Corporation. Do you see that?
A. Yes.
Q. Did in fact the NIH ultimately determine that they had the authority to provide MVA 572 to Therion?
A. Would you repeat that question?
Q. What is your understanding, sir -- do you have an understanding as to whether or not the NIH ultimately determined that they did have the authority to provide MVA 572 to Therion or that they consistently refused to provide it?
A. You're talking about NIH. I was talking about Dr. Moss.
Q. Dr. Moss works at NIH, correct?
A. But from my understanding, NIH as far as I read, learned from the papers, NIH was not involved in

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that.
Q. Okay. Let me --
A. So, therefore, if you allow me.
Q. Sure.
A. I'm referring here that Dr. Moss, and that is also in my supplemental statement, specifically advised Therion that they should give him a written -- that he -- they should ask Professor Mayr for a written permission that he may transfer that material to them. What NIH ultimately sent, as I quoted before, it's exposed. It was not a part of that, to my understanding, agreement.
Q. Is it your understanding that the NIH did in fact ultimately send MVA 572 to Therion?
A. Yes, according to the MTA.
Q. You've seen --
A. They -- I've seen the agreement and they sent to -- not to Therion. I should not mix it. To Acambis or Therion, I'm not aware that they sent anything to Therion, to my understanding. That should be clear.
(Thereupon, a document was marked for

EXHIBIT 8

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAVARIAN NORDIC A/S, Plaintiff, v. ACAMBIS INC. and ACAMBIS PLC, Defendants.	Civil Action No. 05-614 (SLR)

SECOND SUPPLEMENTARY EXPERT REPORT AND/OR LEGAL OPINION OF

PROF. DR. DRES. H.C. JOSEPH STRAUS

In addition to the opinions and testimony, I expressed in my prior statements, I am likely to testify as follows:

1. I recently met with Professor Anton Mayr, in order to confirm my understanding of how, when and where he created various MVA strains, including MVA 572 strain. I did this because I understood that Prof. Mayr is elderly and has given testimony in depositions in the last twelve months which has been used by counsel for Acambis to argue that Prof. Mayr did not own the MVA 572 strain.

2. Prof. Mayr's comments made during the recent meeting support the opinions and facts stated in my prior statements, submitted in this case. Thus, I have relied on my discussion with Prof. Mayr in forming the opinions I hold in this proceeding. This was also the reason why I did not view it necessary to mention my meeting with Prof. Mayr in my Supplementary Statement of November 30, 2006.

German application, but seemingly not in the Swiss one, if the document shown to me correctly reproduces the complete Swiss documents.

6. I would also like to emphasize that according to the German Offenlegungsschrift the title of the respective invention was "Verfahren zur Pockenschutzimpfung" ("Method for Smallpox Vaccination"). This indicates that originally Prof. Stickl applied for a method patent for vaccination and not for a product patent related to strain(s). This would explain my understanding of the role of Prof. Stickl cooperating with Prof. Mayr, namely primarily performing tests with MVA strains produced and owned by Prof. Mayr.

7. Finally, it should be added that neither the German patent document, nor the Swiss document relate to any specifically identified MVA strain, especially not to MVA 572. Thus, apart from the fact that I am convinced, based on the facts which I have learned in the course of these proceedings, that only Prof. Mayr could have been the inventor and the owner of the respective MVA 572 strain, the two patent documents had no bearing as to the tangible ownership of any MVA strain.

8. I have appended to my current statement the German Offenlegungsschrift as it can be downloaded from the Internet. In addition to that also the history of the file as summarized in the official document of the German Patent Office as downloaded, on December 1, 2006, is also appended.

Prof. Dr. Dres. h.c. Joseph Straus

December 6, 2006

EXHIBIT 9

A. Mayr, V. Hochstein-Mintzel, H. Stickl

Origin, Properties and Utilization of the Attenuated Vaccinia Strain MOA

Summary: [see original text in English]

Introduction

The vaccinia virus, together with the variola and alastrim viruses and 8 additional animal smallpox species (cowpox, buffalo pox, rabbit pox, horse pox, elephant pox, mouse pox, monkey pox and camel pox viruses) forms a very uniform virus group of the orthopox viruses that belong to the family of "poxviridae". In their morphological and chemical/physical properties, the orthopox viridae conform to each other to a great extent. According to the usual virus classification they belong to the same serotype (21). Cross immunization against the heterologous smallpox disease is possible with any of the eleven virus types, with the original human and animal smallpox viruses showing better immunization in their respective cases. An exception is made by the vaccinia virus which immunizes uniformly well against all of these illnesses.

The vaccinia virus also possesses the widest host spectrum. Among mammals, cattle, pigs, horses, donkeys, sheep, goats, rabbits, monkeys, buffalo, camels, elephants and zoo animals get infected particularly easily. Natural infections are possible but rare. Usually, the animals get sick in connection with the smallpox vaccination of humans. The infections may lead to a local or generalized illness. The local illness dominates. Generalized vaccinia pox occur preferably in horses, camels, elephants, pigs, rabbits, as well as in young animals.

In contrast, the behavior of the other orthopox viruses is relatively host-specific. Variola and alastrim viruses cause human smallpox, the animal pox viruses cause the respective original smallpox illnesses in cattle, monkeys, camels, etc. While under natural conditions the variola and astrim viruses will not cross over from humans to animals (9), the original animal smallpox viruses, with the exception of the ectromelia virus, can be transmitted to humans through intensive direct or indirect contact. As a rule, they will then lead to benign local illnesses. In the case of highly receptive children and in specially disposed individuals they may also trigger severe general disorders. But independent of the course they may take, they are characterized by their low to absent contagiousness.

So far, effective prophylactic immunization of humans and animals has been possible only through live vaccines. The mechanism responsible for the specific protection seems to be based on the formation of immune cells as well as on humoral defense factors. It would be ideal if we were always able to use the same vaccination virus against all illnesses caused by orthopox viruses without endangering humans, animals and the environment. The vaccinia strains currently used for human smallpox vaccinations do not meet this requirement. The same applies to the strain *Elstree* recommended by the WHO (se above).

Therefore we tried to weaken the vaccinia virus through continuous passages in various cell systems to such a degree that it meets the requirements set forth above, while maintaining its immunological properties. At the same time, we wanted to obtain a vaccination virus that permits parenteral or oral immunization without any negative effects, that induces a quick formation of endogenous interferon when applied locally, that is not contagious for humans and animals, that does not occur in animals under natural conditions and, finally, that allows incubation vaccinations without any posing any danger.

Attenuation of field viruses with the objective of obtaining vaccination viruses for the production of vaccines is not new. Numerous proven live vaccines that today are being used in the entire world in human and veterinary medicine can be retraced to it. Relatively little experiences is available with regard to the attenuation of vaccinia virus and its use as a vaccine, although *Rivers and collaborators* called attention to it as early as in 1931 (23, 24, 26). They passed the vaccinia virus on chorioallantois membrane of chicken embryos. *Kempe* continued these examinations in 1968 and successfully vaccinated eczema patients with such an "egg virus" (12). Attenuation of vaccinia virus via cell cultures has also been tried (1, 3, 4, 13, 22, 23). Each case resulted in changes of certain biological properties that ran parallel with a decrease of virulence for test animals. Recently a compilation of those works was prepared (10).

1. Origin of the MVA Virus and Attenuation

The MVA virus goes back to the dermo-vaccinia strain CVA. It was maintained in Turkey (vaccination institute of Ankara) for many years via donkey-calf-donkey passages, and there it served as the basis for the human smallpox vaccine. As starting material they used the pustule harvest of each respective donkey passage. In 1953, it was purified by us (fractioned ultra centrifugation) and run through two bovine passages (cutaneous area vaccinations), and then introduced in the market in the Federal Republic [of Germany] as smallpox vaccine (8) in the years 1954/55. During that period we examined the CVA virus together with additional domestic and foreign dermo, neuro- and testicular vaccines biologically and serologically for differences in comparison with other animal pox vaccines.

First, we examined the behavior of the individual virus strains in ten-day-old chicken embryos following inoculation of the chorioallantois membrane (CAM) and in rabbits following intracutaneous (i.cut.) and intravenous (i.ven.) inoculation. In the ovum, the CVA virus was very virulent and characterized by

1. flat, sharply contoured primary and secondary foci with a broad, deep central necrosis,
2. 100% 4+ generalization,
3. a tendency to form secondary pox,
4. strong vascular efficacy without hemorrhaging tendency
5. 100% necrosis with relatively early generalization,
6. skin pox in the chicken embryo.

In rabbits, the CVA strain's behavior was reversed. It was relatively tissue friendly. Following intracutaneous inoculation, well defined infiltrates developed without necrosis, without hemorrhage, without secondary pox, in the absence of a generalization and quick retrogression. Intravenous application caused a brief fever (2 to 3 days) without leading to a visible generalization on the skin and the mucous membrane (6, 7).

With intraperitoneal application, the CVA strain led to a generalized pox illness in 3 to 5-day-old mice in the course of which the animals died. On a cellular level, the virus possessed a very wide host spectrum, multiplying itself with high titers and being lytic for all cell cultures (8, 22, 28).

Various vaccinia strains (egg virus, culture virus) agglutinated the same chicken blood corpuscles with different intensity independent of their infectiosity titer. The CVA strain had good hemagglutinating activities (16).

In the application on humans (first-time vaccinees) the CVA strain did not differ from other dermo-vaccinia strains with regard to the vaccinal local and general reactions. The percentage of the various post vaccinal complications was the same as well. However, a significant difference was the tendency of the CVA virus to form secondary pox and the late crust loss in the case of vaccination smallpox. With approximately the same number of first-time vaccinees, 13 cases of secondary pox were reported of strain CVM, 50 cases of strain CVB, but 781 cases of strain CVA in the years 1954/55 in the catchment area of the vaccination institute of Munich (8). Those findings were the reasons for strain CVA being discontinued in the subsequent years for the production of smallpox vaccine at the vaccination institute of Munich.

For our attenuation tests, the CVA strain seemed particularly well suited because of its characteristic biological "marker": tissue friendly behavior in rabbits, quick and strong generalization in incubated chicken eggs, strong and broad central necrosis of the primary and secondary foci on the CAM with relatively low mesenchymal reaction, skim pox in chicken embryos, strong virulence for infantile mice, a broad host spectrum in cell cultures with lysis, good hemagglutinating and immunizing activity and finally, in humans, a tendency for secondary pox and late crust loss of the vaccination pustules.

In 1958, we began with the attenuation tests through continuous passages of the CVA virus (cell-free virus) by means of the final dilution method in various primary cell cultures (tubes containing final virus dilutions). After 300 passages we determined by way of comparative tests that the virus had changed more strongly in the chicken embryo fibroblasts (FHE) culture passages than in the cell cultures from mammal cells (calf and pig kidney cultures). Consequently, we continued to pass the CVA virus in the FHE cultures. For the production of the cultures we used eggs from a poultry farm that was hygienically supervised. Sterile cattle amnion fluid served as medium (technology at *Mayr* and *Kalcher*, 1960 [17]). The virus harvest always occurred at the peak of the cytopathic effect. Of each culture run, non-inoculated control cultures were examined for unwanted virus contamination. In case of doubt the respective passages were rejected. After the 360th passage the virus was cloned in accordance with the plaque method. To this end three consecutive plaque passages were conducted, with the material of the isolation plaque being

tittered out in dilutions in new plaque dishes and dishes with only one plaque (final dilution method) being used again and again for continued passages (20).
In 1963 we examined the 370th/371st passage of the FHE virus morphologically, serologically and biologically in comparison with the CVA starting virus and other dermo and egg vaccinia strains (22). The typical vaccine character had completely disappeared. The FHE passage virus was only morphologically similar to the starting virus. The most conspicuous characteristic was the loss or, respectively, the great reduction of its virulence for rabbits, baby mice and for certain cell cultures. In the chicken embryo CAM inoculation), too, it no longer exhibited typical vaccinia properties. In lieu of flat foci with a deep central necrosis (starting virus) there occurred in the FHE virus small compact proliferation nodules without necrosis. The virulence (vascular damages, involvement of the surroundings, lethal rates) was greatly reduced as compared with the controls while the generalization tendency was kept intact. In the cross neutralization test it was neutralized by specific vaccinia immune sera. Its hemagglutinating activities were reduced. A check for contamination with foreign viruses took a negative course.
Since that time the CVA-FHE virus continues to be passed in FHE cultures. In the meantime it has reached the 570th culture passage and appears to be genetically uniform and stable. The last passages have again been cloned by means of the plaque final dilution method. The eggs used for the plaque dishes came from a recognized leucosis-free poultry stock. After the 516th FHE passage the CVA-FHE virus was given the name MVA virus = Modified Vaccinia Virus Ankara following its clinical tests in humans, because of the stability of its changed properties and in order to prevent its being mistaken for other attenuated vaccinia strains (10, 27).

2. Properties of the MVA Virus

Morphologically and structurally the MVA virus resembles the general structure of the viruses of the orthopox group. Serologically and immune-biologically, too, it belongs to the serotype that characterizes the orthopox viruses. Biologically, however, the MVA virus possesses stable markers that make a differentiation from the other species of the orthopox viruses possible.
The MVA virus can be differentiated from the other vaccinia strains and the remaining species of the orthopox viruses through its pathogenic behavior

1. in the chicken embryo following CAM inoculation = *CHE markers,*
2. in various cell cultures = *TC markers,*
3. in rabbits = *R markers,*
4. in infantile and adult mice = *M markers,*
5. in chickens = *F markers,*
6. in monkeys = *MK markers,*
7. in humans = *H markers*

In addition to the above markers the MVA virus possesses the ability to induce the formation of endogenous interferon in particularly strong fashion. In addition to the formation of interferon there is a great increase of the phagocytose rate. The interferon induction is stronger in the case of administration of large amounts (over $10^{7.5}$ FHE-KID_{50} /ml) than in the case of inoculations with low doses.
The formation of endogenous interferon was reviewed in rabbits. The rabbits were administered intranasally 0.2 ml MVA virus (titer $10^{7.5}$ FHE-KID_{50} /ml) 3 times each in intervals of several hours. Prior to the application and 6, 12, 24, and 48, 72, 96 hours thereafter blood was withdrawn from the animals and the serum (acidification overnight pH 2) was evaluated for its contents of interferon. The evaluation occurred by way of the plaque inhibition test in RK13 cell cultures in accordance with the known method. Sindbis virus, strain AR 86, cultured in the corresponding cell cultures served as test virus. The virus utilization diagnosis amounted to 50 – 80 plaque-forming units. The interferon activity of the samples was measured in interferon units per ml (effective dose 50% =). An ED_{50} is the reciprocal value of the last dilution phase of the test material in which at least a 50% reduction of the number of plaques occurs vis-à-vis the corresponding controls. Prior to the treatment the serum of the animals was negative. After as little as 6 hours, serum interferon values of between 16 and 64 occurred on average. The interferon titers (ED_{50}) then continued to rise continually until the 3rd day and reached values around 256. On the 4th day the titers receded slightly.

In addition to the induction of endogenous interferon we examined the formation of interferon in chicken embryo fibroblast cell cultures following incubation with UV-inactivated, highly passed virus. With the help of vaccinia virus of the high cell culture passages (428th – 458th passage) superior interferon could be produced following the UV inactivation of the same virus quantities than with virus strains of the low culture passages (11th and 12th passage). Interferon from UV-inactivated virus of the high passage reached values of up to 1024 ED_{50}/ml (plaque test with 20 – 50 plaque-forming units) against sindbis virus while the values of UV-inactivated virus of the low passage lay at 64-128 (17).

The increase of the phagocytose rate was examined in the phagocytose test in mice (NMRI mice). The method is based on the determination of the excretion rate of carbon particles from the circulating blood. The animals were inoculated each with 0.3 ml of MVA virus (titer $10^{7.5}$ FHE_E-KID_{50} /ml) i.p. 48 hours later we carried out the test according to the method of *Buschmann* and collaborators (2). The phagocytose index K which indicates the excretion rate of the carbon particles from the blood lay relatively constantly between 0.029 548 and 0.031 089 in the control group (30 animals). In the test animals (3 groups at 30 animals) it increased significantly to 0.04 811 to 0.043 212.

Tables 1, 2 and 3 provide an overview of the various biological markers of the MVA virus.

The MVA virus represents an artificial lab product that does not conform to any of the known, naturally occurring orthopox virus species and that does not exist in nature. It is easy to differentiate from all those virus species. The F marker points at its origin from vaccinia virus and its vaccinia character. Administered cutaneously, the MVA virus causes a mild follicle reaction (circumscribed swelling of the follicles without area) in young chickens (follicle method) that is typical of vaccinia viruses according to *Mayr* (18). In the case of non-attenuated vaccinia strains the local follicle reaction takes a considerably stronger course and occurs in young chicks as well.

Table 1: *CHE and T markers of the MVA virus in comparison with the CVA dermo-vaccinia starting virus*

Markers		MVA Virus	CVA Starting Virus
Type	Reference		
CHE Inoculation of the CAM of 10-day-old chicken embryos, 37°C incubation, Reference value: 4th day p. inf.	*p:* character of the primary foci	A: small, compact proliferation nodules without central necrosis	A: flat foci with deep, broad central necrosis
	n: percentage of the lethal rate	B: 40	B: 100
	g: percentage of the generalization	B: 100	B: 100
	qu: quantity of the generalization	B: + to +++	B: ++++
	op: other properties	Ø	secondary pox, skin pox on the embryo
TC Inoculation of primary cell cultures and cell lines, Reference value: 10^3 FHE_E-KID_{50} /0.1 ml	*fbe:* chicken embryo fibroblasts	V: ++++ L: ++++ CPE: small globules, with granular disintegration	V: ++++ L: ++++ CPE: plaque-shaped degeneration, cell fusion, lysis
	pk: pig kidney cells	V: ++ L: (plaque)	V: ++++ L: ++++
	kk: calf kidney cells	V: ± L: O	V: ++++ L: ++++
	kt: calf testicle cells	V: ± L: O	V: ++++ L: ++++
	h: HELA cells	V: ± L: O	V: ++++ L: ++++

Annotations: A = $10^{-1.5}$ FHE_E-KID_{50} /0.1 ml; B = $10^{3.0}$ FHE_E-KID_{50} /0.1 ml; V = virus multiplication; L = lysis of the cell cultures; CPE = type of cytopathic effect

Table 2: *R, M, F markers of the MVA virus in comparison with the CVA dermo-vaccinia starting virus* (reference value $10^{6.8}$ FHE-KID_{50}/ml)

Markers		MVA Virus	CVA Starting Virus
Type	Reference		
R Rabbit, white Deutsche Riesen *[German giants]* 6 months old	*iv* intravenous 1.0 ml	G Ø	G Ø
	ilk intracutaneous	P Ø	P ++++
	k cutaneous, scarification method, 0.05 ml	P Ø	P ++++
M infantile (1 – 3 days old) and adult mice (12 – 15 g)	*ip* infantile mouse, intraperitoneal, 0.1 ml	M Ø	M 80
	ic infantile mouse, intracerebral 0.05 ml	M Ø	M 100
	ics adult mouse, intracerebral, 0.1 ml	M Ø	M 100
F Chicks and young chickens	*k* cutaneous follicle icon. 0.05 ml	*Chicks:* P Ø *Chickens:* P +	*Chicks:* P +++ *Chickens:* P +++

Annotations: G = percentage of generalization

P = intensity of the primary reaction at the inoculation site
M = percentage of deaths

The most receptive host system for the MVA virus is the chicken embryo following inoculation of the CAM. In the chicken embryo (CHE marker), the MVA virus is characterized by small, compact, often comma-shaped elongated proliferation nodules (primary foci and secondary foci) with a small opaque border without central necrosis. In conformity with its current passing in FHE cultures it has not lost its virulence for the chicken embryo, but it is markedly decreased. Up to the 4th day p. inf., the point in time when the CVA starting virus is 100% generalized with a lethal quota of 100%, only 40% of the embryos have died in the case of the MVA virus, with a generalization quota of 100%. The time until generalization was extended by 20 to 24 hours.

Table 3: *MK and H markers of the MVA virus in comparison with the CVA dermo-vaccinia starting virus* (reference value: $10^{4.8}$ FHE-KID_{50}/ml)

Markers		MVA Virus	CVA Starting Virus
Type	Reference		
MK monkeys, macacus irus, indeterminate age	*ik* 0.2 ml	P Ø	P ++++
	k 0.05 ml	P Ø	P ++++
	b buccal 0.1 ml	P Ø	P ++++
	ith intrathalamic 0.1 ml	MB Ø	MB 100
H humans, first-time vaccinees	*ik* 0.2 ml	P + redness, mild infiltration up to 20 mm	P ++++ strong reaction with formation of pustules and necroses
	i.m. intramuscular, 0.2 ml	P Ø	not examined
	k incision inoculation	P Ø	P ++++ strong normal first-time inoculation reaction

Annotations: see Table 2

MB = percentage of illnesses

The quantity of generalization is contingent on the inoculation virus amount. In the case of inoculation doses under 10^2 KID_{50} is +, in the case of inoculation amounts of over 1,000, on the other hand, it is +++. It has lost its ability to cause secondary pox and skin pox in the embryo. In Illustrations 1 and 2 the various chorioallantois membrane pictures of the primary and secondary foci are shown between the CVA starting virus (Illustration 1) and the MVA virus (Illustration 2).

On the cellular level (CTC markers), the most conspicuous characteristic of the MVA virus is the great restriction of the host spectrum. The MVA virus is fully virulent only for chicken embryo fibroblast cultures. In this, it differs from the CVA starting virus by the quality of the cytopathic effect. Like the other vaccinia virus strains, the CVA starting virus leads to a lysis of the infected cell cultures via a plaque-shaped degeneration (areal propagation of the infected cells) together with cell fusions. A typical globulization phase is absent (Illustration 3). In the case of the MVA virus, on the other hand, it comes to a globalization (very small and irregular globules) of the infected cells that later disintegrate granularly, with the grayish cell detritus remaining intact (Illustration 4). This is particularly conspicuous in the plaque test (cf. Table 1).

The MVA virus has completely lost its vaccinia character in rabbits (R marker) and mice (M marker) as well. In rabbits, cutaneous and intracutaneous inoculations will not lead to any primary reaction at the inoculation site, and if administered intravenously, it will not come to any generalization.

In mice, the most conspicuous characteristic is the loss of neuro-virulence. Neither infantile (1 – 3 days old) nor adult mice (12 – 15 g) became ill following intracerebral application. Generalization is absent following intraperitoneal inoculation of 1 – 3-day-old baby mice (cf. Table 2).

Macacus monkeys (MK marker) infected cutaneously, intracutaneously and buccally do not show any primary reaction. Intrathalamically infected monkeys do not get sick, while 100% of the monkeys infected with the starting virus CVA and other vaccinia viruses do fall ill (cf. Table 3). Finally, the great loss of virulence of the MWA *[sic]* virus is particularly conspicuous in humans (H marker). The usual cutaneous incision or point inoculation takes a negative course with regard to any primary reaction at the inoculation site. MVA virus administered intramuscularly does not cause any local reaction, either. Only following intracutaneous application does it come to a mild infiltrate formation at the inoculation site that is clearly outlined against its surrounding, of up to 20 mm with a reddening of the area. The reaction quickly recedes without loss of substance and scab formation (cf. Table 3). General reactions are absent.

The MVA virus has not changed with regard to antigen structure and immunogenic properties. It is neutralized in a purified state (through fractioned ultracentrifugation) by specific vaccinia immune sera regardless of their origin. But because of its great loss of virulence for mammals it has an active immunogenic effect in the vaccinee only if it is administered repeatedly in high concentrations (over $10^{7.5}$ $FHE\text{-}KID_{50}$. In this respect the MVA virus behaves similarly to an inactivated virus, however with the difference that, in addition to the formation of antibodies, it also stimulates the formation of immune cells that are essential for a smallpox immunity. A precondition for a successful vaccination is good resorption of the virus.

[illustration]

Illustration 1: Chorioallantois membrane – Image of the primary and secondary foci in the CVA starting virus: 4th day.

[illustration]

Illustration 2: Chorioallantois membrane – Image of the primary and secondary foci in the CVA starting virus: 4th day post inf.

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For that reason, parenteral, oral, intranasal or intracutaneous application of the MVA virus enhance the immunization success better that cutaneous administration.

3. Application of the MVA Virus

The MVA virus is suited for active immune prophylaxis against all illnesses caused by orthopox viruses in humans and animals. Due to its low virulence and its strong and quick induction of the formation of endogen interferon, emergency inoculations can be performed with the MVA virus without any risk. The MVA virus dos not possess any contagiousness. Therefore, humans and animals can not transmit the virus to receptive individuals regardless of what application modus was used in the inoculation.
The harmlessness of the MVA virus for pets that are considerably more sensitive in comparison to humans was proved in newborn sterile, gnotobiotically obtained animals and in conventionally newborn animals.
For the tests with the gnotobiotic animals we used piglets obtained through caesarean section under sterile conditions. They were immediately transferred to an isolator system and fed sterile feedstuff. From their birth on they were administered orally (via the milk) $10^{7.2}$ FHE-KID_{50} MVA viruses daily over a period of 10 days. Untreated controls ran parallel under the same conditions. The animals were hygienically supervised, the weight increase was examined and compared and conventionalized step by step after two weeks. A total of 26 piglets were afflicted with the MVA virus in this manner. None of the animals became sick or showed deviations from the norm. The weight increase in the case of the MVA-inoculated animals was slightly better than that of the controls. The vaccinees tolerated the conventionalization equally well as the control animals, too. Development and condition of the vaccinees was even better than in the untreated piglets.
In addition to this test we afflicted conventionally newborn calves, piglets and dogs with the MVA virus in the same dosage as above. The calves and piglets received the virus orally (via their feed or per stomach tube) for several days (2 to 10 times daily), the puppies were inoculated once orally or intraperitoneally, respectively. During the inoculation period, all animals remained with their mothers and siblings which included non-vaccinated newborns for control purposes.

[illustration]

Illustration 3: Cytopathic effect in the case of CVA starting virus in chicken embryo fibroblast cultures: 2nd day post. inf.

[illustration]

Illustration 4: Cytopathic effect in the case of MVA virus in chicken embryo fibroblast cultures: 2nd day post. inf.

Overall, 18 newborn piglets, 100 newborn calves and 10 newborn puppies were inoculated. No animal became sick, control animals were not put at risk. In addition we inoculated two 14-day-old piglets intravenously with 5 ml of MVA ($10^{5.0}$ KID_{50}/ml). The animals tolerated the dose without any reaction. Again and again mouse breeding farms are threatened by ectromelia entities. For a year we have been vaccinating prophylactically several of those test animal breedings (over 1000 stock animals per breed)

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with MVA against mouse pox. All female and male parent animals aged 3 weeks and older are vaccinated. The inoculation occurs intraperitoneally with 0.2 ml of vaccine. The vaccine receives $10^{7.5}$ FHE-KID_{50}/ml. Vaccination occurs 1 time per year. Vaccination illnesses and vaccination ruptures via ectromelia field virus infestation did not occur. The animals developed normally.

Elephants kept in captivity are particularly susceptible to vaccinia and cowpox infections. They get ill in generalized fashion, with a high lethality rate. A smallpox outbreak in elephants (5) in the area of Stuttgart during which animals fell ill in generalized fashion, with the older elephant dying, caused us to vaccinate the remaining eight animals, predominantly young ones, prophylactically with the MVA virus following characterization of the pathogen as a vaccinia virus (two contact cases in humans). This involved, without any doubt, an incubation vaccination or, respectively, an emergency vaccination. Per animal, 2 ml of vaccine ($10^{7.0}$ FHE-KID_{50}/ml) was applied subcutaneously at the ear base. The animals tolerated the vaccination well. Neither local nor general reactions occurred. No animal contracted smallpox during the subsequent period. In the meantime, based on this experience, six young elephants at the zoo of Gelsenkirchen and eight elephants at the zoo in Berlin were vaccinated in the same manner as described above. The animals in Berlin were given 5 ml subcutaneously in lieu of 2 ml. All animals overcame the vaccination without any complications. One animal at the Berlin zoo developed a fist-sized swelling at the vaccination site. A local abscess caused by contamination during the vaccination process is suspected.

In addition to the indications above we have vaccinated eight horses, ten head of cattle and six sheep subcutaneously with MVA virus (2.0 ml, $10^{7.8}$ FHE-KID_{50}/ml). No animal exhibited any local or general reactions. Finally, we used the MVA virus as a biological interferon inducer in so-called problem stock of calves. In some cattle breeding operations the exists a hospitalism that leads to a high mortality rate of newborn calves during their first weeks. Most often it is a mixed infection involving in particular E. coli, Pasteurella, staphylococci, and entero, rhino, adeno and REO viruses. The 1 – 4-day-old calves were given 5 ml of MVA virus ($10^{7.5}$ FHE-KID_{50}/ml) orally via their milk 1 to 2 times in intervals of 24 hours. No animal showed any postvaccinal reactions. Mortality and morbidity could be significantly reduced.

We have reported separately on the application of the MVA virus in humans (29).

References

[see original]

EXHIBIT 10

CONTAINS CONFIDENTIAL BUSINESS INFORMATION
SUBJECT TO PROTECTIVE ORDER

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C.

Before the Honorable Robert L. Barton, Jr.
Administrative Law Judge

In the Matter of

CERTAIN MODIFIED VACCINIA ANKARA ("MVA") VIRUSES AND VACCINES AND PHARMACEUTICAL COMPOSITIONS BASED THEREON

Inv. No. 337-TA-550

INITIAL DETERMINATION ON VIOLATION OF SECTION 337 AND RECOMMENDED DETERMINATION ON REMEDY AND BONDING

(September 6, 2006)

In general, infection of an individual with a virus in the form of a vaccine is done with the intention of conferring immunity to a disease. Generally, the virus is specially prepared and/or packaged for sale and/or use as a vaccine, for example by growing the virus under otherwise sterile conditions, drying the preparation to a powder form, and packaging the dried powder in a sterile, sealed container. Viruses can also be stored in frozen form. Pharmaceutically acceptable carriers, diluents, and/or additives may be included at this point or may be added afterwards in preparation for administration of the virus/vaccine to a patient. JSF ¶ 18.

5. The Science of MVA

a. Genome Structure

The genome of MVA is comprised of double stranded DNA approximately 178 kilobases (kb) in length. RX-143 at B003473. The two ends of the genome contain inverted terminal repeats (ITR) of approximately 9.8 kb. Id. at B003491. These ITRs do not encode for any known MVA protein. Id. at B003491-B003492. ITRs may play a role as recognition points for DNA replication machinery, but there is no scientific evidence that ITRs contribute to viral phenotype. Drillien, Tr. at 642:22-643:20; Carroll, Tr. at 1286:17-21. The portions of the genome which are not located in the ITRs encode the proteins produced by an MVA virus. RX-143 at B003474-B003490. The '893 patent defines the "functional part" of the MVA genome as "a part of the complete genomic sequence that encodes a physical entity, such as a protein, protein domain, or an epitope of a protein . . . [and] parts of the complete genomic sequence that code for regulatory elements." '893 patent at 8:63-9:1. Thus, the '893 patent (and the '752 patent which shares a similar specification) equates the "functional part" of the MVA genome with the non-ITR portions of the genome.

b. Sequence Data

Only one MVA strain of record, MVA-M4 (the "Antoine" strain), has had its entire genome, both the coding region and ITRs, sequenced. RX-143. The M4 strain is a plaque-purified clone of MVA 575. Id. at B003497; RX-650, Carroll Wit. Stat. at 161:14-19. The sequence of the coding region of both MVA-BN and MVA 3000 is also on record. CX-62. An alignment of the three coding regions of these sequences shows: 1) that the MVA-BN and MVA 3000 sequences are identical, and 2) that the "Antoine" sequence differs from those of MVA-BN and MVA 3000 at five base pairs. CX-62.

Subsequent resequencing of these five base pairs of the M4 strain has demonstrated that the original sequence was erroneous. RX-254; RX-255; RX-256. With these corrections to the sequence data, the coding regions of M4, MVA-BN, and MVA 3000 are identical. Although Dr. Drillien testified that the corrections to the originally published M4 sequence suggest that other errors may be present in that sequence, no evidence of any other errors has been produced. Drillien, Tr. at 670:7-12. However, Dr. Drillien testified that with respect to the five nucleotides, the data was reliable. Id. at 672:15-18. Dr. Carroll found the resequencing data convincing evidence that the DNA sequences of the coding regions of all three strains were identical. Carroll, Tr. at 1233:22-1239:13. Additionally, Dr. Chaplin concluded from the same data that the three sequences are identical. Chaplin, Tr. at 368:8-369:16. Dr. Drillien also testified that showing identity between the coding regions is sufficient to show identity between the genomes of two viruses. CX-243, Drillien DWS at 81:6-10.

Based on the DNA sequencing data of record and the testimony of both expert and fact witnesses, I find that the coding regions of M4, MVA-BN, and MVA 3000 are identical. Because identity between the coding regions is sufficient to find identity between viral genomes, I also find that the genomes of M4, MVA-BN and MVA3000 are identical.

c. The Relationship of Genotype and Phenotype

There is little dispute that genotype, the genes comprising the genome of a given virus, directly correlates to the phenotype, the biological properties, of that virus. Drillien, Tr. at 788:15-21. Thus, viruses with identical genomic sequences will exhibit the same functional properties. Id. at 790:5-10; Id. at 818:11-12 ("Two viruses that have the same sequence have the same properties."); see also Carroll, Tr. at 1239:4-5 ("if the sequences are identical, then the phenotypes will be the same"). Additionally, it is the coding region of the MVA genome which determines phenotypic characteristics of the virus. CX-243, Drillien DWS at 81:11-18 (stating that if two MVA viruses have identical genomic sequences in their coding region "it is extremely likely, if not obvious, that they will be the same, that they will display exactly the same phenotypes"), 81:19-82:3 (stating that there is a "99.9 percent" likelihood that two viruses with identical sequences in the coding region "are the same viruses with respect to their characteristics in any biological test you might perform"); Drillien, Tr. at 652:17-23; Carroll, Tr. at 1286:17-1287:2.

While the experts agree that genotype is directly related to phenotype, Dr. Drillien also testified that it is important to consider that the DNA sequence for a given virus represents the majority of genomes within that virus population. Drillien Tr. at 811:16-22. Dr. Drillien stated the opinion that MVA, and pox viruses in general, can have high degrees of variability in a population.

Id. at 813:17-25. Dr. Drillien testified that "it's possible that there can be minority genomes for which the sequence has not been determined which still contribute to the phenotype, to the properties of that virus population." Id. at 811:22-812:1. Dr. Drillien testified that, because of the presence of the minority populations which possibly affect phenotype, he "would draw the conclusion that one cannot correlate perfectly the sequence and the properties of the virus." Id. at 820:10-12; compare Drillien, Tr. at 818:11-12 ("Two viruses that have the same sequence have the same properties.") Dr. Drillien provided no indication of how a minority virus population could affect phenotype. Dr. Carroll, commenting on Dr. Drillien's theory that a minority virus population could affect phenotype stated, "in some strange process, the virus transformed with a new phenotype that somehow kept the identical sequence to the prior art . . . . I couldn't really understand the virological explanation for that." Carroll, Tr. at 1285:17-21. Additionally, while Dr. Drillien testified that it is scientifically feasible to sequence a minority strain, no such evidence has been produced in this investigation. Drillien, Tr. at 813:17-25. To the contrary, Dr. Carroll testified that the one sequence for which the underlying raw data was produced (the resequencing of the M4 genome), showed no evidence of containing "minority strains." Carroll, Tr. at 1358:3-1359:9.

The experts agree that it is the genotype of the coding region of MVA viruses which determines the phenotypic characteristic of the MVA virus. Dr. Drillien stated that it is possible that minority genomes in a heterogenous virus population may play a role in determining the phenotype of that virus population. Drillien, Tr. at 811:22-812:1, 820:10-12. However, Dr. Drillien neither explained how this possibility might occur nor provided any basis for this hypothesis. Without clear evidence supporting his hypothesis, in addition to his conflicting testimony on this particular issue, I find Dr. Drillien's testimony on this issue to be unreliable. Furthermore, even if Dr. Drillien's

hypothesis is correct, it would only be applicable to heterogenous, not homogenous, populations. Therefore, the evidence shows that there is a direct correlation between the sequence of the MVA coding region and the phenotypic characteristics of the MVA virus.

d. Virus Replication Assays

The viral replication assays at issue in this investigation all follow a similar format. The methodology disclosed in the '893 and '752 patents is illustrative of this format and the most relevant to this investigation. That procedure is as follows:

> For infection the cells were seeded onto 6-well-plates at a concentration of $5x10^5$ cells/well and incubated overnight at 37°C., 5% CO_2 in [cell culture medium] with 2% FCS [fetal calf serum]. The cell culture medium was removed and cells were infected at approximately moi [multiplicity of infection] 0.05 for one hour at 37°C., 5% CO_2 (for infection it is assumed that cell numbers doubled over night). The amount of virus used for each infection was $5x10^4$ $TCID_{50}$ and is referred to as Input. The cells were then washed 3 times with [tissue culture medium] and finally 1 ml [tissue culture medium], 2% FCS was added and the plates were left to incubate for 96 hours (4 days) at 37°C., 5% CO_2. The infections were stopped by freezing the plates at -80°C; followed by titration analysis.

'752 patent at 17:21-32. The method disclosed by the '893 and '752 patents for titration analysis involves: 1) extracting the MVA viruses from the initially-infected cells; 2) preparing different dilutions of the virus; 3) inoculating the different dilutions onto cells which support replication of the virus, e.g. CEF cells; 4) incubating the cells, and; 5) measuring the level of cytopathic effect on the permissive cells. Id. at 17:35-61. The titration assay allows the determination of the amount of virus in a particular sample. Drillien, Tr. at 696:6-11.

1. Assay Variability

3. This ID shall become the determination of the Commission 45 days after its date of service unless the Commission within those 45 days shall have ordered review of this ID, or certain issues herein, pursuant to 19 C.F.R. § 210.43(d) or § 210.44.

Robert L. Barton, Jr.
Administrative Law Judge

Issued: September 6, 2006

EXHIBIT 11

CONFIDENTIAL EXHIBIT

EXHIBIT 12

CONFIDENTIAL EXHIBIT

EXHIBIT 13

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EXHIBIT 14

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EXHIBIT 15

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EXHIBIT 23

CONFIDENTIAL EXHIBIT

EXHIBIT 24

Prof.Dr.Dr.h.c.mult. Anton Mayr
Institut für Med. Mikrobiologie,
Infektions- und Seuchenmedizin
der Tierärztlichen Fakultät
Veterinärstr. 13
D-80539 MÜNCHEN

München, den 19.09.95

An
Dr. Bernard Moss
Laboratory of Viral Diseases
Building 4, Room 229
National Institutes of Health
Bethesda, MD 20892-0455

Dear Mr. Moss,

Thank you for your interest in our MVA-strain.
We are able to send you some samples of our
- seed virus and
- vaccine.

1) seed virus: "MVA"
2 vials: 575. FHE-Pass. v. 14.12:83
2 ml (freeze-dried)

2) vaccine: "Vacc.-Virus MVA"
3 vials: II/85
1 ml (freeze-dried).

Sincerly yours,

Prof. Dr. Dr. h.c. mult. Anton Mayr
Lehrstuhl für Mikrobiologie
und Seuchenlehre
Veterinärstraße 13
80539 München

EXHIBIT 25

EXHIBIT 7

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Laboratory of Viral Diseases, NIAID
National Institutes of Health
Building: 4, Room: 229
4 Center Drive, MSC 0445
Bethesda, MD 20892-0445
Phone: 301-496-9869; Fax: 480-1147
Email: bmoss@nih.gov

August 3, 2001

Prof. Anton Mayr
Lehrstuhl für Mikrobiologie und Seuchenlehre
Ludwig-Maximilians-Universitat Munchen
Veterinaerstr. 13
80539 Muenchen
GERMANY

Dear Prof. Mayr,

Gerd Sutter told me the good news that you have been able to locate an early sample of MVA in your freezer and have agreed to send it to me. I wish to thank you for your generosity in this regard. As you are aware, MVA has taken on a new life as the premier vaccinia virus vector. I have enclosed a reprint of a recent paper that clearly illustrates the great potential value of MVA.

I understand that Gerd will help with the shipping of the MVA. He has also indicated that he is willing to help with a draft of a letter of authentication of the MVA in order to satisfy the regulatory agencies here.

Again, I thank you for your kindness in this matter.

Sincerely yours,

Bernard Moss

Bernard Moss M.D., Ph.D.
Chief, Laboratory of Viral Diseases

cc: Dr. Gerd Sutter

EXHIBIT 26

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EXHIBIT 27

CX-262C:1

EXHIBIT 14

Prof.Dr.Dr.h.c.mult.Anton Mayr
Lehrstuhl für Mikrobiologie und Seuchenlehre
Ludwig-Maximilians-Universität München

80539 München
Veterinärstraße 13
Tel. 089/2180-2532

12. September 2001

Bernard Moss M.D., Ph.D.
Chief, Laboratory of Viral Diseases
NIAID, National Institutes of Health
Building 4, Room 229
Bethesda, MD, 20892-0445
USA

Dear Professor Moss,

In response to your request for an early sample of vaccinia Virus MVA I was happy to provide you with the material MVA 572. FHE - 22.02.1974.

This virus material represents lyophilized tissue culture material from the 572nd passage of MVA on primary chicken embryo fibroblasts harvested February 22, 1974 and originates from the vaccinia virus MVA developed and passaged at the Institut für Mikrobiologie und Infektionskrankheiten der Tiere, Ludwig-Maximilians-Universität München (see Mayr *et al. 1975, Passage history, pro partus and applicability of the attenuated vaccinia virus strain MVA*, Infection 3:6-14).

Propagation in chicken embryo fibroblasts through two plaque purification passages (MVA 569.FHE - 12.02.74 and MVA 570. FHE - 15.02.74) and an amplifying passage (MVA 571. FHE - 19.02.74) resulted in the virus stock MVA 572. FHE - 22.02.1974 which was titrated (original titer $10^{8.25}$ $TCID_{50}$/ml) and lyophilized as standard MVA seeding material. This virus material has been stored at the institute under my control since that time.

With best regards.

Sincerely yours,

Dr. Mayr

Prof.Dr.Dr.h.c.mult.Anton Mayr

TOTAL P.02

EXHIBIT 28

EXHIBIT 13

Received by BN A/S 04 JUN 2003

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

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23 April 2003

Prof. Dr. Dr. h.c. mult. Anton Mayr
Lehrstuhl fur Mikrobiologie und Seuchenlehre
Veterinarstrasse 13
80539 Munchen
GERMANY

Dear Professor Mayr,

At the request of Dr. Michael Mowatt, Director of the Office of Technology Development at the National Institute of Allergy and Infectious Diseases (NIAID), I have not previously responded to your letter to me, dated 6 November 2002, regarding "MVA and uses thereof." Dr. Mowatt's request stemmed from the very positive meeting held on 8 January 2003 meeting in Bethesda, Maryland with Drs. Peter Wulff and Paul Chaplain of Bavarian Nordic A/S. I understand that the 8 January meeting, which included Drs. John La Montagne, Carole Heilman and Pamela McInnes as well as Ms. Cindy Fuchs and Dr. Mowatt of the NIAID, yielded fruitful discussion of the respective positions of the NIAID and Bavarian Nordic in regard to NIAID's use and distribution the MVA 572.FHE – 22.02.1974 that you provided to me in late summer 2001. Specifically, I understand that Drs. Wulff and Chaplain were to relay to you the amicable conclusions reached during the meeting. In this context I was both surprised and disturbed by Dr. Wulff's letter, dated 27 March 2003, to Dr. John La Montagne of the NIAID (enclosed). For this reason I feel it necessary at this time to address the inaccuracies reflected in your 6 November 2002 letter to me.

Dr. Gerd Sutter brought the F6 isolate of MVA to the National Institutes of Health (NIH) after he received an AIDS scholarship from the Bundesministerium für Forschung und Technologie to work in my laboratory. In 1992, Dr. Sutter and I reported that MVA expressed both vaccinia viral and recombinant proteins at a high level in non-permissive human cells and suggested that MVA would make a safe and efficient vector for vaccines [Sutter and Moss, PNAS 89, 10847,1992]. These claims were substantiated in a series of animal protection experiments over the next several years [for example: Sutter et al. Vaccine, 12, 1032, 1994; Wyatt et al. Vaccine 14, 1451, 1996; Carroll and Moss Virology 238, 198, 1997; Durbin et al Vaccine 16, 1324, 1998; Wyatt et al. Vaccine 18, 392, 1999; Stittelaar et al. J. Virol. 74. 4236, 2000; Amara et al. Science 292, 69, 2001; Earl et al. Virology 294, 270, 2002]. Although the F6 strain was perfectly good for "expression vector work" in the laboratory, it did not have a well-documented passage history. I contacted you in 1995 to request MVA from an original vial of either a vaccine lot or a master seed for the purpose of producing recombinant vaccines for clinical use. In response to my request you generously provided MVA 575 and MVA II/85 without any restrictions. Because the U.S. Food and Drug Administration had expressed concern about the theoretical possibility that the causative agent of bovine spongiform encephalopathy (BSE) was a contaminant in MVA preparations made in the 1980's, I

subsequently requested a vial of an earlier lot. In response to my request you generously provided MVA 572 in the summer of 2001, again with no restrictions. I never received MVA from the European tissue culture collection or from Bavarian Nordic, and therefore am not aware of any restrictions or licenses that you may have placed on the distribution of materials provided to these organizations.

In your 6 November 2002 letter to Dr. La Montagne, you expressed concern regarding the safety profile of the MVA that you provided to me. I must assume that your concerns arose after you shipped MVA 572 to me, as you failed to mention any such concerns whatsoever in the letter, dated 12 September 2001, that you provided to me in response to my request for documentation about the MVA 572 you shipped in the summer of 2001. Nevertheless, I assure you that, before testing in clinical trials any derivatives of MVA 572, the NIAID will undertake, at a minimum, all testing necessary to meet safety standards mandated by clinical regulatory authorities.

I am enclosing a package of reprints describing my studies over the years with MVA. You will see that I have referenced your publications numerous times in order that you receive recognition for your seminal work. I believe that we are all striving toward the goal of enhancing the health and security of the peoples of the world.

Sincerely yours,

Bernard Moss

Bernard Moss M.D., Ph.D.
Chief, Laboratory of Viral Diseases
Division of Intramural Research, NIAID

Enclosures

cc: P Wulff, Bavarian Nordic A/S, via facsimile transmittal: +45 33 26 83 80 without enclosures
J La Montagne, Deputy Director, NIAID without enclosures
M Mowatt, Office of Technology Development, NIAID without enclosures
S Sherman, Office of the General Counsel, NIH without enclosures
M Rohrbaugh, Office of Technology Transfer, NIH without enclosures

A. Mayr
23 Apr 2003

TOTAL P.

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EXHIBIT 30

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